STUDIES ON PAIN MANAGEMENT: PREEMPTIVE ANALGESIA AND TRADITIONAL CHINESE MEDICINE (TCM)

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STUDIES ON PAIN MANAGEMENT: PREEMPTIVE ANALGESIA AND TRADITIONAL CHINESE MEDICINE (TCM)

Summary

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". This definition reflects pain as a complex sensory and subjective experience, which exists in the context of functional, physical, psychological, cognitive, emotional and social dimensions. Pain represents a major primary healthcare problem and is a very common complaint presented by several patients. The focus of our research is on pain management from two perspectives:

(1) Assessment of "preemptive analgesia" for postoperative pain in an animal model and a pilot clinical study,

(2) Survey of the use of Traditional Chinese Medicine (TCM) for ambulatory acute or chronic pain management in Singapore.

The effective management of postoperative pain is considered to be a major challenge, which often falls short of expectations. Basic scientific evidence suggests that analgesic intervention before surgery may yield a better outcome than the same intervention made after surgery. We explored in this study the concept of "preemptive analgesia" as, an anti-nociceptive treatment that prevents the establishment of altered processing of afferent input that amplifies postoperative pain, by conducting an animal study and a small-scale clinical study. The preemptive analgesic effects of

etoricoxib, celecoxib, indomethacin, naproxen and tramadol were studied in a rat model of post-incisional pain. The findings thus obtained indicated that animals given preoperative administration of these drugs exhibited significantly higher ($P< 0.05$) withdrawal thresholds than that of the placebo control group. Moreover, the effects of preoperative administration of etoricoxib, indomethacin, naproxen or tramadol were significantly higher ($P< 0.05$) compared to that of postoperative administration of the corresponding drug for a period up to 2 days after the surgery.

A clinical study was then conducted to compare the analgesic efficacies and safety profiles of preoperative rofecoxib with preoperative tramadol in patients undergoing haemorrhoidectomies at an ambulatory surgical centre. Both rofecoxib and tramadol showed similar analgesic efficacies in this study. However, tramadol was associated with a higher incidence of side effects.

With the growing popularity of Complementary and Alternative Medicine (CAM), a study was needed to provide a better understanding of TCM use in pain management. A questionnaire was designed and administered to investigate the importance of TCM in acute and chronic pain management. The main objective was to establish the prevalence of and the common reasons for its use by patients attending consultations at two primary healthcare settings – the family/polyclinic and the TCM clinic, where the western/conventional medical doctor and the TCM practitioner practiced, respectively. This survey, which included 214 respondents (98 from TCM practitioner clinic and 116 from polyclinic), revealed that the prevalence of TCM use to treat pain problem in the preceding 12 months was approximately 47%, and about half (46.5%)

of these respondents, who were mostly Chinese, used TCM as the first-line treatment for pain relief. This suggests that TCM is more than just an alternative medicine in Singapore, and perhaps also in other countries, where there are ethnic Chinese.

The three different studies described above looked into various aspects in pain management. Although some limitations in study design were noted, it serves as a platform for further research to provide better understanding in pain management. Future study with proper study design, preferably double blind study with representative sample size, would be required to give useful information in pain management.

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List of Abbreviations

5-HT	5-Hydroxytryptamine
ANOVA	Analysis of Variance
CAM	Complementary and Alternative Medicine
CHM	Chinese herbal medicines
CMC	Carboxymethyl cellulose
CMM	Chinese Medicinal Materials
CNS	Central nervous system
COX	Cyclooxygenase
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
coxibs	Cyclooxygenase-2 inhibitors
CPM	Chinese proprietary medicines
g	Gram
hr	Hour
i.p.	Intraperitoneal
IASP	International Association for the Study of Pain
MAOIs	Monoamine Oxidase Inhibitors
mg	Milligram
mg/kg	Milligram/Kilogram
min	Minute
ml	Milliliter
MOH	Ministry of Health
NRS	Numerical Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
op	Operation
p	*p*-value
PG	Prostaglandin
PGE2	Prostaglandin E-2

SD	Standard Deviation
SGH	Singapore General Hospital
$t_{1/2}$	half-life
TCM	Traditional Chinese Medicine
TCMP Act	Traditional Chinese Medicine Practitioner's Act
TM	Traditional Medicine
t_{max}	Time to the maximum concentration
VRS	Verbal Rating Scale
v/v	Volume/volume
w/v	weight/volume
WHO	World Health Organization

Chapter I – Introduction

1.1 General introduction

Pain hurts and we all have experienced some kind of pain at some times in our lives. It serves as an early warning that alerts individual to the presence of damaging stimuli, nonetheless persistent pain in most of the cases serves no additional purpose than causing excessive stress and suffering. Several studies have recognized pain as a major primary health care problem and it represents the most commonly perceived symptom which has an enormous impact on public health. Population studies in Finland and Sweden reported pain as the reason for 40% and 30% of visits to primary care practice [1, 2]. A group of researchers had reported that pain prevalence was as high as 78% in the Spanish general population [3].

Pain has been defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [4]. This definition reflects pain as a complex sensory and subjective experience, which exists in the context of functional, physical, psychological, cognitive, emotional and social dimensions.

The classification of pain is diverse. According to the nature of pain, it can be roughly divided into two groups: physiological pain and clinical pain [5]. Physiological pain is initiated by specialized sensory nociceptor fibers innervating peripheral tissues and activated only by noxious stimuli. It is normally short in duration and represents a

warning system for potentially harmful stimuli [5, 6]. Clinical pain is initiated by tissue damage or inflammation; it is related to activation of the nociceptive afferents as part of a disease or trauma [5, 6]. On the other hand, from a temporal point of view, pain can then be classified as acute and chronic [7, 8]. Pain immediately following an injury to the body is considered to be acute. It may be self-limiting in some occasions and typically subsides when the injury heals. However, acute pain problems are the most frequent reasons for patients seeking medical attention and are commonly observed in emergency room care, the postoperative setting, obstetric practice, sports medicine and the care of trauma and burn patients [9]. IASP has defined chronic pain [10] as "pain without apparent biological value that has persisted beyond normal tissue healing time (usually taken to be 3 months)." Unlike acute pain which instructs the individual to avoid further injury or seek help, chronic pain usually serves no benefit to the individual. It is often destructive to the host by deteriorating quality of life, functional ability, financial status et cetera [7].

Pain sensation involves a series of complex interactions between peripheral nerves and the central nervous system (CNS). Nociception, or the sensation of pain, is composed of four basic processes: transduction, transmission, modulation, and perception. These processes are modulated by excitatory and inhibitory neurotransmitters and psychological and physiological responses to stimuli. The goal of pain management is to reduce peripheral sensitization, thereby decreasing central stimulation and the amplification associated with wind-up, spread, and central sensitization. This often requires multiple modalities to interrupt transmission at different levels [7, 11]. Figure 1.1 shows the various neuronal pathways as well as

potential sites for prevention and treatment in pain management [12]. Inadequately treated pain can induce physiological hormonal responses that alter circulation and tissue metabolism; can produce major psychological stress responses and compromise the body's immune system. Thus, pain should be managed or treated aggressively [7].

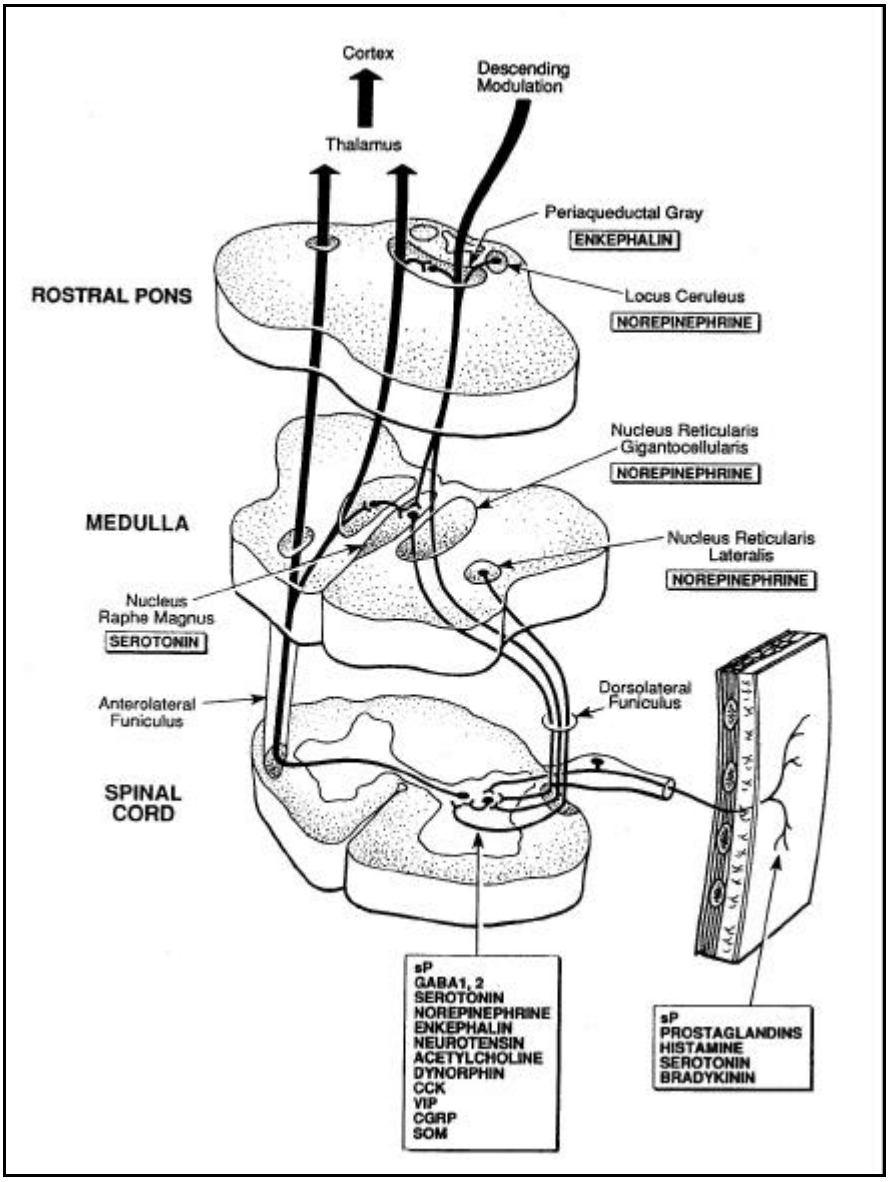

Figure 1.1 Neuronal pathways and potential sites for prevention and treatment in pain management. Broadly, the potential sites of action are brain; spinal cord neurons; dorsal root and peripheral nerve axon; and peripheral nociceptors/inflammatory response mediators. Some of the endogenous neurochemical mediators of nociception are listed in the figure, which represents potential pharmacologic option in pain management [12].

1.2 Prevalence of postoperative pain and its impact

It is widely perceived that pain is part of the package of surgery. Although pain is an unavoidable but predictable part of the postoperative experience, inadequate management of postoperative pain is common with profound implications [13]. Several clinical practice guidelines or reports [13-15] for improving postoperative pain management are available, but studies continue to show an embarrassing lack of progress in this direction. It was noted nearly 30 years ago that approximately 73% of patients reported moderate-to-severe pain following medical and surgical procedures [16]. A Gallup poll conducted in 1995 in United States revealed that 54% of all patients reported unsatisfactory postoperative analgesia [17]. Another recent United States National Survey revealed that approximately 80% of patients experienced acute pain after surgery, and about 86% of them reported moderate, severe, or extreme pain. It was also noted in the same survey that 'experiencing postoperative pain' was the most common concern (59%) of patients undergoing surgery [13].

The consequences of poor postoperative pain management are considerable. Unrelieved postoperative pain is often associated with clinical and psychological changes that have significant impact upon morbidity and mortality, as well as, financial costs and quality of life. Furthermore, pain has pathophysiological effect on body systems that may lead to an increased incidence of myocardial ischemia, atelectasis, and impaired wound healing [13, 16]. Therefore a need to develop new medications, new multimodal therapies, new dosing strategies and new surgical approaches to provide better postoperative pain management is pressing.

1.3 The concept of preemptive analgesia

In the beginning of the last century, Crile was among the first to introduce the concept of treating pain prior to its onset: preemptive analgesia [18, 19]. Woolf [20, 21] then paved the idea that preemptive analgesia might reduce the magnitude and duration of postoperative pain in 1983. Crile advocated the use of regional blocks in addition to general anesthesia to prevent intraoperative nociception and the formation of painful scars caused by changes in the central nervous system during surgery [19]. The resurgence of this idea was associated with a series of animal studies started by Woolf, who showed evidence for a central component of post-injury pain hypersensitivity in experimental studies [20, 21]. Initial observations indicated that noxious stimuli induced changes in neural function [20, 22], such as hyperexcitability, in the spinal cord. This idea was then further highlighted by Wall [23] in a 1988 editorial that drew clinicians' attention because it linked fundamental work to clinical studies [22, 23]. The editorial related the findings in fundamental studies, the changes in the central nervous system that followed nociceptive stimuli and the ways in which these changes could be preempted, to clinical work in postoperative pain.

An overwhelming amount of experimental data had demonstrated that various antinociceptive techniques applied before injury were more effective in reducing the post-injury central sensitization phenomena compared with administration after injury [19, 24]. This convincing finding in experimental research has triggered many clinical studies and systemic reviews of clinical studies [21, 22, 25-30]. It is currently concluded that although the experimental research provided very promising evidence on

preemptive analgesia, results of clinical studies regarding the value of preemptive analgesia are still controversial.

The definitions of preemptive analgesia are far from being uniform, and therefore cited as the major cause of controversy regarding its clinical relevance [19, 24, 30]. There are as many as three different definitions employed in the recent clinical trials [19]:

1. Starts before surgery;
2. Prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery);
3. Prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period).

Kissin has reviewed these definitions and given his support to definition 3 which is then widely accepted [19, 30] and thus adopted in our studies. Tissue damage will inevitably produce two phases of sensory input, the first will be associated directly with the tissue-damaging stimulus, i.e. during surgery, and the second will result from the inflammatory reaction to the damaged tissue [25]. Since both phases of nociceptor input have the capacity to induce altered sensory processing (central sensitization), the ideal preemptive treatment, therefore, should cover the entire duration of central sensitization, from the primary phase well into the postoperative period [19, 30]. The most important conditions for establishment of effective preemptive analgesia are the establishment of an effective level of antinociception before injury, and the

continuation of this effective analgesic level well into the post-injury period to prevent central sensitization during the inflammatory phase [30].

The idea of preemptive analgesia is attractive, especially true when the management of postoperative pain has been criticized over the last 30 years, despite the advent of increasingly high-technology approaches. If preemptive analgesia worked, improvement in patient comfort, decrease in postoperative morbidity and potential healthcare saving could be anticipated [21, 30].

1.4 Cyclooxygenase inhibitors

The cyclooxygenase (COX) enzyme catalyses the first step in the conversion of arachidonic acid to prostanoids (prostaglandins and thromboxanes) (Figure 1.2). The COX enzyme exists in at least 2 distinct isoforms; a largely constitutive form termed COX-1, which plays a role in platelet aggregation, homeostasis, and the protection of gastric mucosa; and a largely inducible isoform termed COX-2, which is a crucial mediator of pain, inflammation, and fever [16, 31].

Cyclooxygenase inhibitors, both selective and non-selective inhibitors, act by inhibiting prostaglandin synthesis. Prostaglandin (PG) is the primary noxious mediator released from injured tissues which is responsible for activation of primary afferents and sensitization of nociceptors to secondary and tertiary mediators (substance P, bradykinin, and histamine). Both forms of COX regulate the synthesis of PG in general. However, PG synthesized by COX-2 activity (primarily PGE2) mediates a pain response that includes inflammation; the specific interruption of the

COX-2 pathway disrupts this process, and thus the primary noxious mediator can be blocked and the action of second- and third-order downstream mediators may be reduced [16]. Moreover, the expression of COX-2 enzyme in the dorsal horn neurons, induced by inflammation and nerve injury, is believed to contribute to neuronal plasticity and central sensitization. This suggests that cyclooxygenase inhibitors should have a more active role in treatment of postoperative pain [6, 32-34].

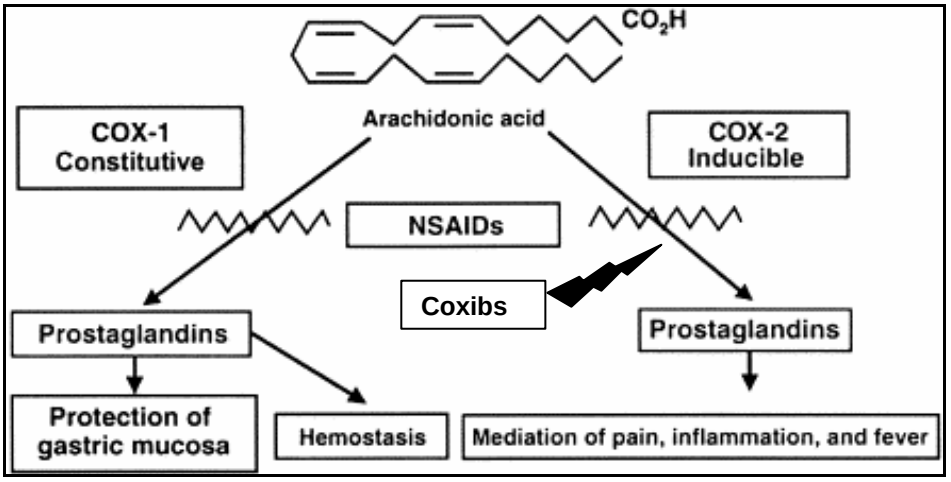

Figure 1.2 Cyclooxygenase pathways and mechanism of action of coxibs and NSAIDs. COX-1, a constitutive enzyme, plays a major role in the release of PG to protect gastric mucosa and regulate homeostasis. COX-2, an inducible enzyme, releases PG that mediates pain, inflammation, and fever. Nonselective NSAIDs inhibit both forms of COX, while coxibs selectively inhibit COX-2, resulting in control of pain and inflammation with a minimal effect on bleeding and gastric mucosa [16].

1.4.1 NSAIDs or non-selective COX inhibitors

Non-selective NSAIDs inhibit both isoforms of COX enzyme. The inhibition of COX-2 activity has more direct implication in ameliorating inflammation, whereas, the inhibition of COX-1 enzyme has been related to adverse effects commonly seen in NSAIDs. The major side-effects of NSAIDs treatment are well documented and include gastrointestinal toxicity (such as perforation and bleeding), impaired homeostasis, and depression of renal function. However, it is suggested that the incidence of such side-effects is very low in the context of short-term postoperative pain treatment [34-37].

NSAIDs have been widely used in postoperative pain management as single-or multimodal-regimen. It has been proven to be reliable for relieving postoperative pain after minor procedures, such as, dental surgery and episiotomy [38]. When given concurrently with opioids, NSAIDs have reduced postoperative opioid consumption by 17-40% and patients have benefited from an earlier return of postoperative bowel function and a lower incidence of bladder spasm [34, 39].

1.4.2 Selective COX-2 inhibitors (coxibs)

Specific inhibitors of COX-2 or the selective COX-2 inhibitors (coxibs) were developed with the aim of maintaining analgesic and anti-inflammatory efficacies that is similar to traditional, non-selective NSAIDs, but avoiding the gastrointestinal complications associated with the inhibition of COX-1 enzymes (Figure 1.2) [17, 40, 41]. At physiological doses, the coxibs selectively inhibit only COX-2, thus minimizing the adverse effects mediated through inhibition of COX-1 [42]. Currently available

clinical data suggested that the coxibs demonstrated clinical efficacy equivalent to that of NSAIDs in the treatment of pain and inflammation, while keeping the gastric and coagulation side-effects to a minimum [33, 34, 43, 44]. Nevertheless, coxibs do not offer a clinically relevant advantage over the non-selective group with regards to the renal adverse effect and concerns over the cardiovascular risk of coxibs have been raised recently [43, 45].

1.5 Tramadol

Tramadol hydrochloride is a centrally acting, synthetic analgesic with two distinct, but complementary, mechanisms of action: a weak opioid agonist with selective affinity at the μ- opioid receptors; and a weak inhibitor of the reuptake of noradrenaline (norepinephrine) and serotonin [46]. Its main advantages over conventional opioids – sparseness of opioid-related side effects such as respiratory depression, constipation, tolerance and dependence, has made it a favorable choice for postoperative pain, refractory cancer pain, chronic inflammatory disorder and neuropathic pain [47].

1.6 Animal models of pain

Animal models play a critical role in the understanding of human pain. Several animal models had been introduced to replicate painful clinical condition with which to examine pathogenic mechanisms and explore therapeutic options, e.g. hot plate test, tail flick test, formalin test et cetera. However, the utility of the knowledge derived from these studies is fully dependent on a close match of the model to human disease [48]. It has been suggested that neither pain caused by chemical irritation nor

neuropathic pain models operate on a time scale that parallels the clinical operative and postoperative states. Furthermore, pain from a surgical incision is usually occurring at rest and is exacerbated by coughing, ambulation, and mechanical stimulation, thus mechanical sensitivity is an important property of a surgical incision. It is therefore suggested that the efficacy of postoperative analgesic treatments should be assessed using evoked responses during function if outcome is to improve with enhanced analgesia [49, 50].

In order to advance the knowledge of postoperative pain and gain a better understanding of the mechanisms of pain from an incision, a new model of postoperative pain involving rats was introduced in 1996 by Brennan et al., and validated pharmacologically by Zahn et al., [49, 51, 52]. This model demonstrated reproducible and quantifiable mechanical hyperalgesia, which can last for several days after the incision. It was reported that the duration of mechanical hyperalgesia in this model is similar to the period of mechanical sensitivity and evoked pain from coughing observed postoperatively in humans. This animal model of incisional pain should allow understanding in mechanisms of sensitization caused by surgery and facilitate investigation of novel therapies for postoperative pain in humans [49].

1.7 Complementary and Alternative Medicine (CAM)

Traditional, complementary and alternative medicines (CAM) are becoming increasingly popular with more frequent use throughout the world and gaining acceptance in the healthcare system [53]. The World Health Organization (WHO) Traditional Medicines Strategy 2002-2005 [54] has therefore, reviewed the status of

Traditional Medicine (TM)/ Complementary and Alternative Medicine (CAM) globally; and defined its role in TM/CAM by developing a strategy to address issues of policy, safety, efficacy, quality, access and rational use of traditional, complementary and alternative medicines. According to the report, the use of TM remains widespread in developing countries, while the use of CAM is increasing rapidly in developed countries. In Malaysia, a developing country, traditional forms of Malay, Chinese and Indian medicines are used extensively; it is estimated that, US$500 million is spent annually on TM/CAM compared to about US$300 million on allopathic medicine [(54)]. On the other hand, the percentage of the population, which used CAM at least once, is 75% in France, 70% in Canada, 48% in Australia and 42% in United States [(54)].

WHO defines Traditional Medicine as "including diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness." This definition encompasses the various commonly used Traditional Chinese Medicine (TCM) therapies, for example, Chinese herbal medicines (CHM) and acupuncture. TCM can be considered the most common form of unconventional treatment, especially among the majority ethnic Chinese in Singapore. The use of TCM has become part of local lifestyle as it is common practice to incorporate Chinese Medicinal Materials (CMM) into daily meals or beverages, for example soups, herbal tonic or herbal tea to build up body resistance to disease, to restore health during convalescence or to raise energy levels.

In a study carried out in 1994 by the Ministry of Health, Singapore (MOH) [55], about 45% of Singaporeans had consulted a TCM practitioner in the past, with the highest proportion among the Chinese (54%), and a much smaller proportion of Malays (8%) and Indians (16%). About 12% or 10,000 of daily outpatient attendance were estimated to be seen by TCM practitioners. The Traditional Chinese Medicine Practitioner's Act (TCMP Act) was passed in November 2000 by the Singapore Parliament. The Act requires TCM practitioners who practise the prescribed practice of TCM to be registered and issued with a license to practise. As at June 2003, a total of 1701 were registered as TCM practitioners and/or acupuncturists under the Register of TCM practitioners, as compared to 6231 western physicians who registered with the Singapore Medical Council [56]. From these figures, it appears that TCM is an established alternative medicine in Singapore.

1.7.1 The role of CAM in pain management

Several studies have engaged in analyzing the use of CAM therapies alone or in conjunction with conventional therapy in pain complaints. The prevalence of CAM used in pain management varies from 5.9% to 40.3% in different settings [3, 57-59]. Although patients' satisfaction varies from study to study, CAM seems to be a frequent option for many patients [60]. It was found that acupuncture, massage and herbal remedies were the more popular treatments used. In the Singapore setting, study carried out by MOH [55] found that out of a total of 2530 respondents, 30% consulted a TCM practitioner for sprains and 18% for aches and pains. Hence, pain problems appear to be commonly presented to TCM practitioners in Singapore.

1.7.2 Terminology

TCM refers to raw herbs, ready-made herbal products for oral consumption or external use, acupuncture and Chinese massage therapy used in the system of therapeutics according to traditional Chinese method. Ready-made products refer to patent herbal products either for oral consumption or external use, and medicated plasters with herbal ingredients.

Conventional medicine is a medical science that is rooted in Greek philosophy. It is considered by many as mainstream medicine, Western medicine or modern medicine. It is the basis of Singapore's primary and secondary health care system. Practitioners of this branch of medicine are called conventional doctors. They are trained in the universities, medical schools and hospitals where they are taught clinical medicine, basic medical sciences and clinical skills.

CMM [55] can be grouped into the following 2 categories:

1. Raw CMM are substances which are used in their natural states. They may have been subjected to simple processing like cutting and drying.
2. Chinese proprietary medicines (CPM) are CMM that have been formulated into finished products in the form of tablets, pills, mixtures, et cetera. They contain only ingredients derived from CMM and are not allowed to contain western chemicals/drugs.

1.8 Aims of study

Pain is a very common complaint presented by patients, and it represents a major primary healthcare problem which is worthy of more attention. Hence, the focus of our research is on pain management from two perspectives:

(1) Assessment of "preemptive analgesia" for postoperative pain in an animal model and a pilot clinical study,

(2) Survey of the use of Traditional Chinese Medicine (TCM) for ambulatory acute or chronic pain management in Singapore.

An animal experimental study in rats was designed to compare the preemptive analgesic properties of three different classes of analgesics, namely NSAIDs, COX-2 inhibitors and tramadol. Five different drugs were chosen in this study, celecoxib, etoricoxib, indomethacin, naproxen and tramadol. The second clinical study looked into the analgesic efficacy of preoperatively administered rofecoxib and tramadol in haemorrhoidectomy patients. The third questionnaire survey investigated the prevalence of and common reasons for the use of TCM to treat pain problem and patient perceptions on the use of conventional analgesics and/or TCM for pain.

Chapter II – Animal study: The preemptive analgesic effect of celecoxib, etoricoxib, indomethacin, naproxen and tramadol

2.1 Hypothesis

The role of oral NSAIDs, coxibs and tramadol in preemptive analgesia has not been extensively studied, especially in the rat model of incisional pain. We hypothesized that by utilizing a more appropriate animal model of incisional pain, the preemptive analgesic effect of celecoxib, etoricoxib, indomethacin, naproxen and tramadol would be better demonstrated. This animal study was designed to evaluate the preemptive analgesic effects of five drugs, celecoxib, etoricoxib, indomethacin, naproxen and tramadol, in the rats' model of incisional pain. In addition, the time-effectiveness and dose-effectiveness investigation of etoricoxib when administered preoperatively at different times or different doses were also carried out.

2.2 Materials and Methods

The experimental protocols were reviewed and approved by the Laboratory Animals Center, National University of Singapore. The animals were treated in accordance with the Ethical Guidelines for Investigations of Experimental Pain in conscious animals as issued by the International Association for the Study of Pain [61].

Experiments were performed on adult male Sprague-Dawley rats (weight 250-300g). Before the surgery, animals were housed in pairs with free access to food and water. Postoperatively, the animals were housed individually and the incision was checked

daily; any sign of wound infection or dehiscence excluded the animal from the study. All animals were euthanised at the end of the protocol.

2.2.1 Surgery

Skin incision surgery was performed as previously described by Brennan et al., (Figure 2.1) [49, 52] with minor modification. All rats were anaesthetized with a mixture of fentanyl/fluanisone and midazolam (2.7ml/kg i.p.) and the plantar surface of the left hind paw was prepared in a sterile manner with 10% v/v povidone-iodine solution. A 1-cm longitudinal incision was made with a number-11 blade, through skin and fascia of the plantar aspect of the foot, starting 0.5 cm from the proximal edge of the heel and extending toward the toes. The plantaris muscle was elevated and incised longitudinally. Following homeostasis with gentle pressure, the skin was opposed with two single interrupted sutures using 5-0 mersilk sutures. The wound site was covered with gentamycin antibiotic cream and the animals were allowed to recover individually in a cage.

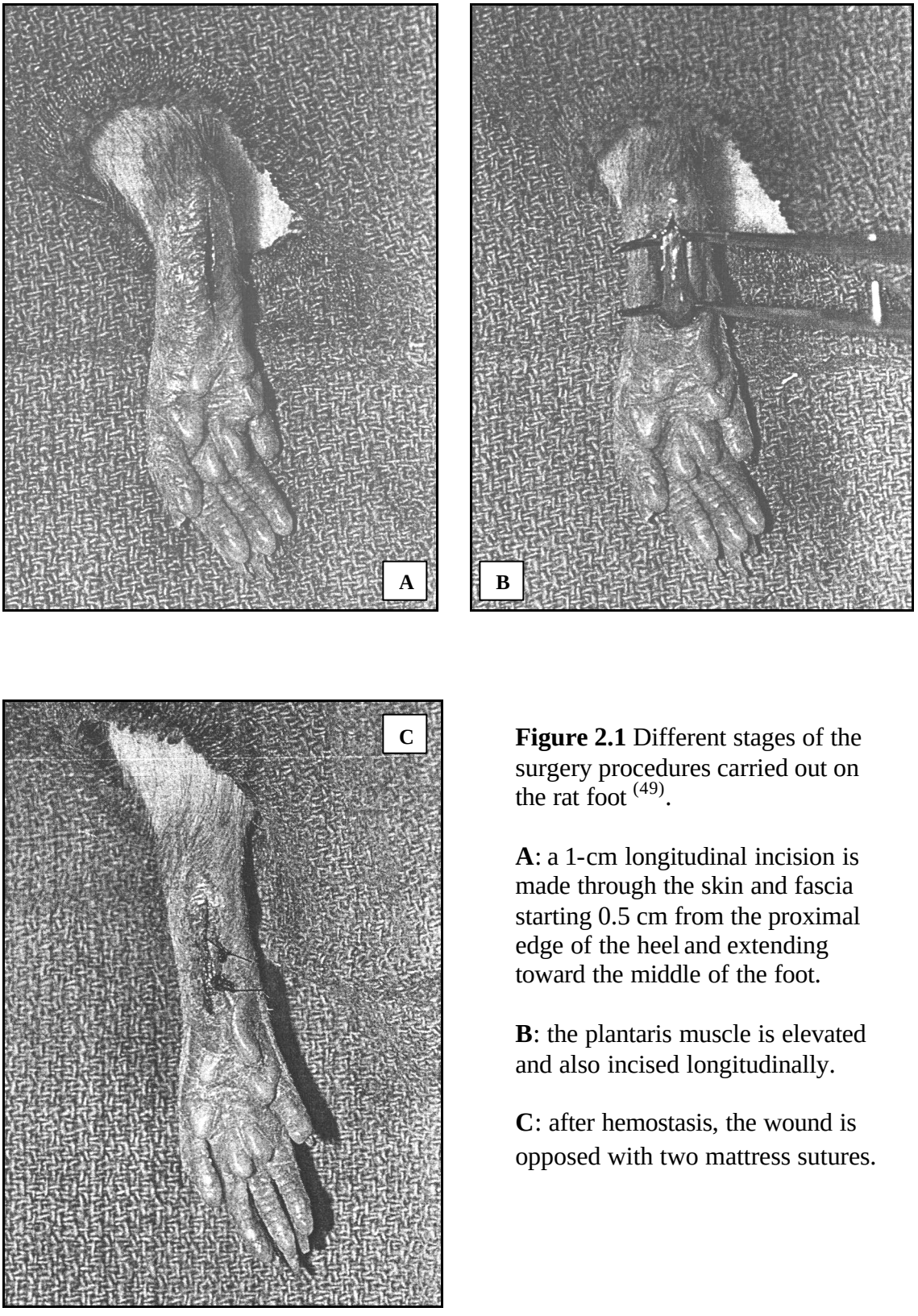

Figure 2.1 Different stages of the surgery procedures carried out on the rat foot [(49)].

A: a 1-cm longitudinal incision is made through the skin and fascia starting 0.5 cm from the proximal edge of the heel and extending toward the middle of the foot.

B: the plantaris muscle is elevated and also incised longitudinally.

C: after hemostasis, the wound is opposed with two mattress sutures.

2.2.2 Postoperative testing

Withdrawal responses to mechanical stimulation. Mechanical allodynia was measured with an automated dynamic plantar Von Frey apparatus (Dynamic Plantar Aesthesiometer, UgoBasil, Italy. Figure 2.2). The rats were placed individually on an elevated framed metal mesh floor covered with two-compartment plastic enclosure. Following acclimation, a stainless steel filament of 0.5 mm diameter was electronically delivered to the plantar hindpaw from underneath the cage to an area adjacent to the wound and to the same area on the non-injured foot. The filament was pushed against the hindpaw with ascending force, ramping from 0-50 gram over a 10-second period. When the animal responded to the stimulus by withdrawing its hindpaw, the mechanical stimulus was automatically withdrawn and the force at which the animal responded was recorded. The cut-off value, 50 g, was recorded even if there was no withdrawal response to this force. Measurements were repeated twice with a 3-5 min test-free period between each trial. The withdrawal threshold was determined by the average of these 3 measurements. The animals were tested before surgery (Baseline), at 4 hr after surgery (4 hr Day 0), and once daily for 3 days postoperatively (Day 1, Day 2 and Day 3).

Pain score. A numerical pain scoring system was developed to further assess the pain behavior (Appendix I). The scale was developed by adapting from several measures that had been used in other studies [62-64], which was then customized to fit our protocol. The observation parameters include the appearance (general grooming, eyelid closure, ocular/nasal discharge), behavioral changes (biting/licking of the

wound, vocalization, overall activity, provoked activity), clinical sign (diarrhea/abnormal discharge), body weight changes and weight bearing score [49]. The observation was done when the unrestrained animals were placed on an elevated enclosure as described above, 4 hr after surgery and once daily for 3 days postoperatively. The cumulative pain score (0-25) provides an indication of the overall well-being of the animal. The higher the score, the more likely it is that the animal was experiencing severe pain.

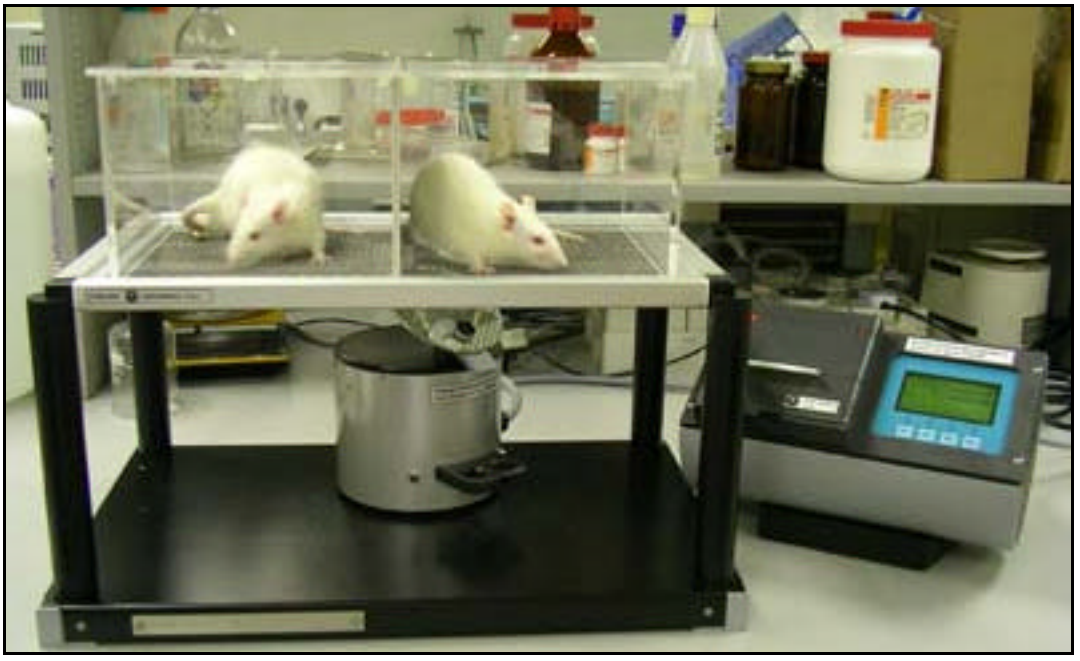

Figure 2.2 Dynamic Plantar Aesthesiometer, UgoBasil, Italy

2.2.3 Experimental groups

The experiment was divided into three phases. In phase one, preemptive analgesic effects of 5 drugs, celecoxib (30 mg/kg), etoricoxib (30 mg/kg), indomethacin (30 mg/kg), naproxen (30 mg/kg) and tramadol hydrochloride (40 mg/kg) were evaluated. These doses were selected from those used in other studies [65-68]. Animals were allocated randomly to different drug groups with 5-6 animals per group. The drugs were suspended in carboxymethyl cellulose (CMC) 0.5% w/v solution and administered orally by gastric gavage in a volume of 1 to 1.5 ml. The control group received a placebo 1 hr before and 2 hrs after surgical incision; the preoperative group received the active drug 1 hr before and placebo 2 hr after surgery; whereas the postoperative group received placebo 1 hr before and active drug 2 hr after surgery. Phase two involves a time-effectiveness testing where etoricoxib (30 mg/kg) was administered at different time-points preoperatively (1 hr, 12 hr, 1 day [2 doses: 24 hr and 1 hr before] and 2 days [3 doses: 48 hr, 24 hr and 1 hr before]). In phase three, the dose-effectiveness testing, different doses of etoricoxib (10, 20 and 30 mg/kg) were administered 1 hr pre-operatively.

2.2.4 Statistical analysis

Statistical software SPSS 11.0 for windows was employed in all statistical tests. Data analysis was performed using the untransformed data of withdrawal threshold and cumulative pain score. Data were analyzed by analysis of variance (ANOVA) followed by post hoc Bonferroni correction analysis. In any situation, $P = 0.05$ is considered statistically significant.

2.3 Results

2.3.1 Preemptive analgesic effect between different drugs

Figure 2.3A- 2.3E compares the withdrawal responses of the five different drugs to mechanical stimuli generated by the von frey apparatus, namely celecoxib 30 mg/kg, 30 etoricoxib mg/kg, indomethacin 30 mg/kg, naproxen 30 mg/kg and tramadol 40 mg/kg, given before and after operation, respectively. As can be seen from the data obtained, the incision of the plantar surface of the hind paw produced a significant reduction in the withdrawal threshold, with the lowest point located at 4 hrs after operation (4 hr Day 0) and gradually recovering towards the pre-incision baseline value. Before the surgery, the rats exhibited baseline withdrawal thresholds which ranged from 45.95 ± 3.01 to 48.95 ± 0.95. Similar results were obtained when applying the filaments against the plantar aspect of the non-operated hind paw. The tested drugs reduced, but did not abolish the post-incisional mechanical allodynia. In each experimental group, the withdrawal threshold of animals treated 1 hr before operation was significantly higher than that of the control group at all observation time-points (except celecoxib at Day 2, and naproxen at Day 3). The effects of tramadol given preoperatively were significantly higher than that of the postoperative group at four observation points; whereas those given indomethacin and naproxen showed differences up to 2 days after surgery; and those on etoricoxib showed differences at Days 1 and 2 after the procedure. On the other hand, no significant difference was found between the threshold of the control group and postoperatively-treated group with the exception of indomethacin at Day 2.

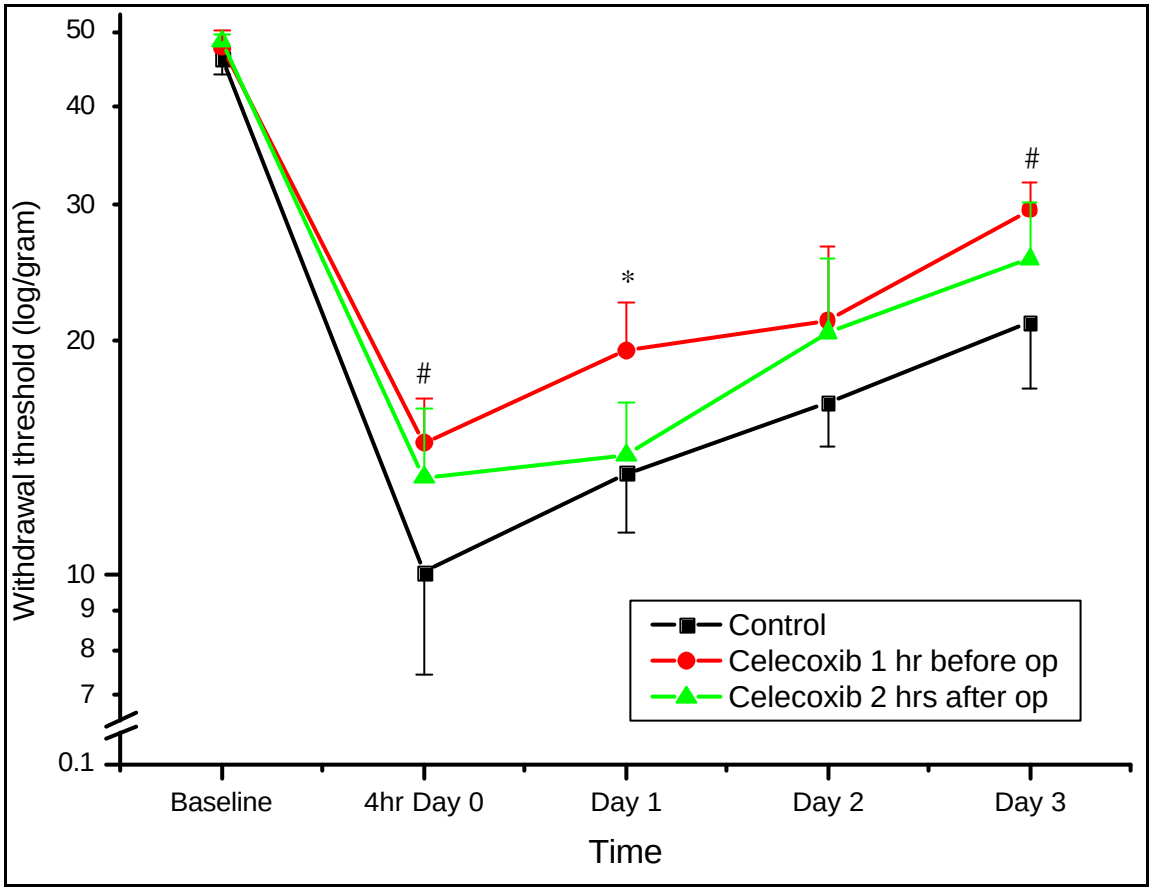

Figure 2.3A Effects of celecoxib (30mg/kg), given 1 hr before operation and 2 hrs after operation, on the paw withdrawal threshold in response to mechanical stimuli in rats. The withdrawal threshold of animals treated 1 hr before operation was significantly higher than that of the control group at all observation time points except at Day 2 (P = 0.032, 0.003, 0.004 for 4 hr Day 0, Day 1 and Day 3 respectively). Significant difference was found between the before and after operation group at Day 1 with P = 0.009. No significant difference was found between groups at Day 2.

** $P < 0.05$ for before operation vs. all groups*
 # $P < 0.05$ for control vs. before operation
The forces are in grams and expressed as means ± SD.

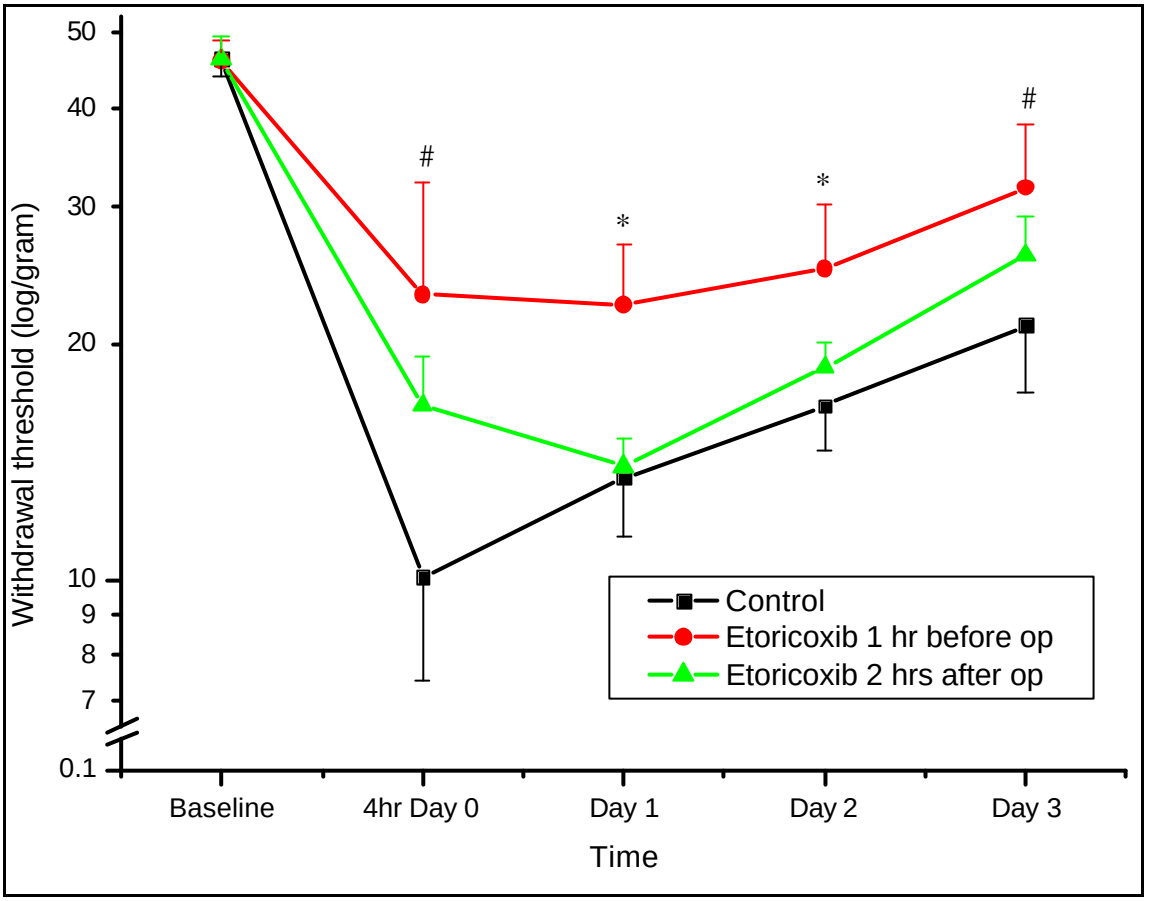

Figure 2.3B Effects of etoricoxib (30mg/kg), given 1 hr before operation and 2 hrs after operation, on the paw withdrawal threshold in response to mechanical stimuli in rats. The withdrawal threshold of animals treated 1 hr before operation was significantly higher than that of the control group at all observation time points (P = 0.004, 0.001, 0.002 and 0.006 respectively). Significant difference was found between the before and after operation group at Day 1 and Day 2 with P = 0.001 and 0.016 respectively.

** $P < 0.05$ for before operation vs. all groups*
 # $P < 0.05$ for control vs. before operation

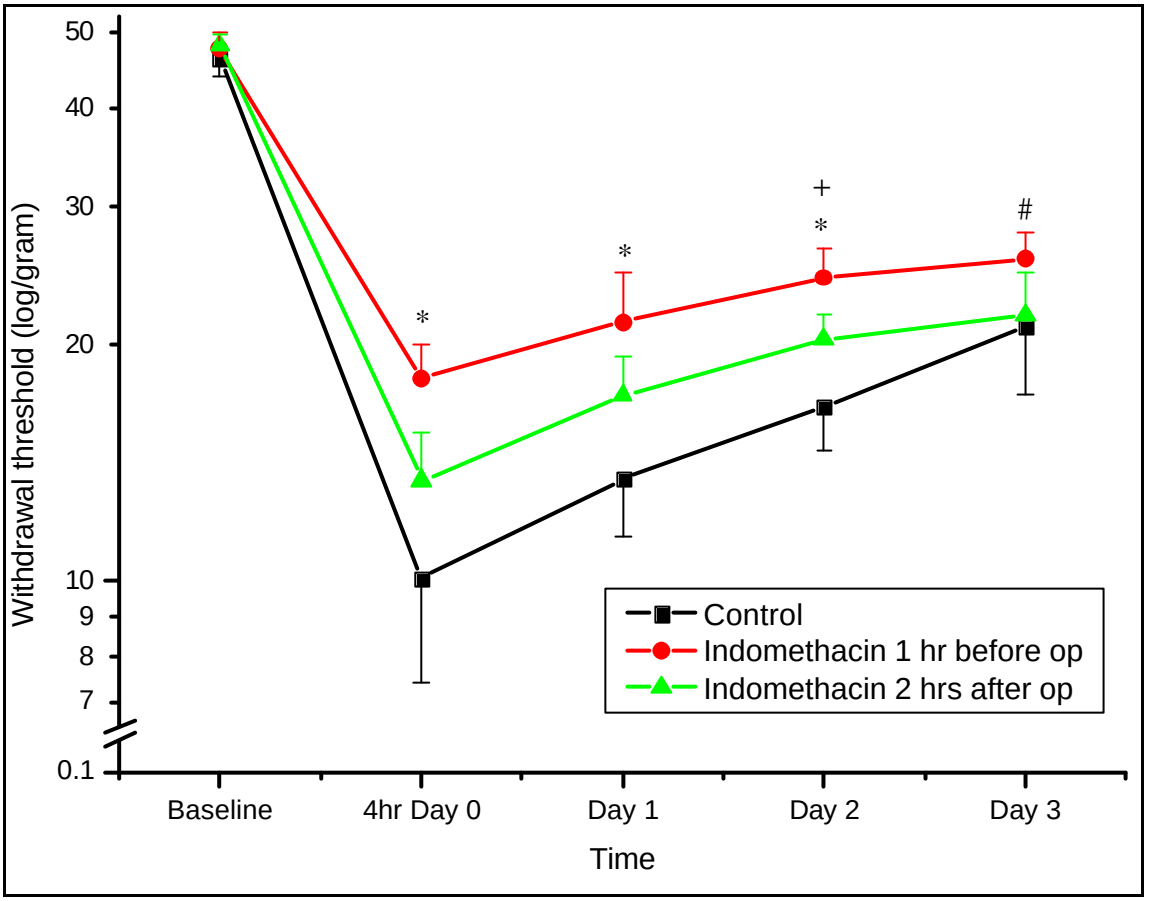

Figure 2.3C Effects of indomethacin (30mg/kg), given 1 hr before operation and 2 hrs after operation, on the paw withdrawal threshold in response to mechanical stimuli in rats. The withdrawal threshold of animals treated 1 hr before operation was significantly higher than that of the control group at all observation time points (P = 0.001 for 4 hr Day 0, Day 1 and Day 2, and P = 0.05 for Day 3). Significant difference was found between the before and after operation group at 4 hr Day, Day 1 and Day 2 with P = 0.007, 0.043 and 0.009 respectively. Besides, significant difference was also found between the control and postoperation group at Day 2 with P = 0.016.

** $P < 0.05$ for before operation vs. all groups*
 # $P < 0.05$ for control vs. before operation
+ $P < 0.05$ for control vs. after operation

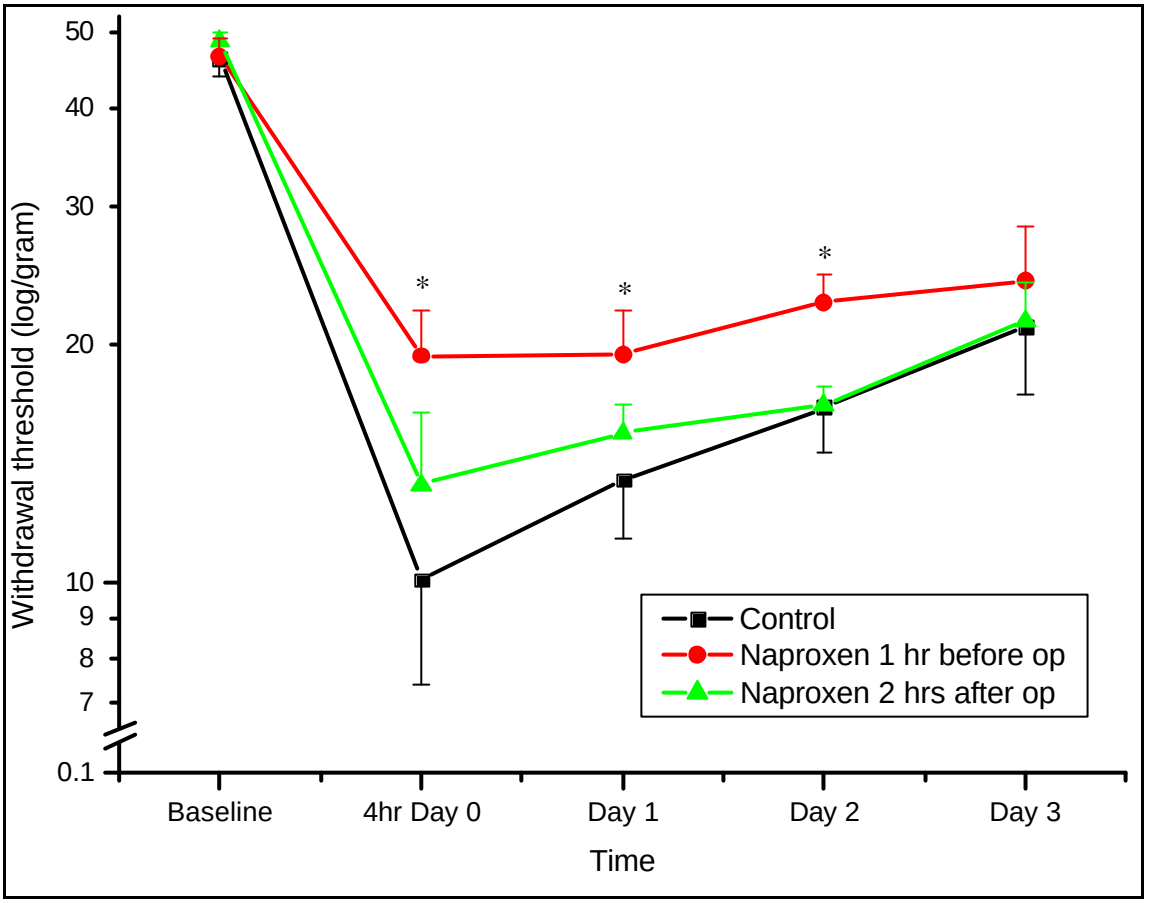

Figure 2.3D Effects of naproxen (30mg/kg), given 1 hr before operation and 2 hrs after operation, on the paw withdrawal threshold in response to mechanical stimuli in rats. The withdrawal threshold of animals treated 1 hr before operation was significantly higher than that of the control group at all observation time points except at Day 3 (P = 0.001 for 4 hr Day 0, Day1 and Day2). Significant difference was found between the before and after operation group at 4 hr Day, Day 1 and Day 2 with P = 0.007, 0.014 and 0.001 respectively. No significant difference was found between groups at Day 3.

** $P < 0.05$ for before operation vs. all groups*

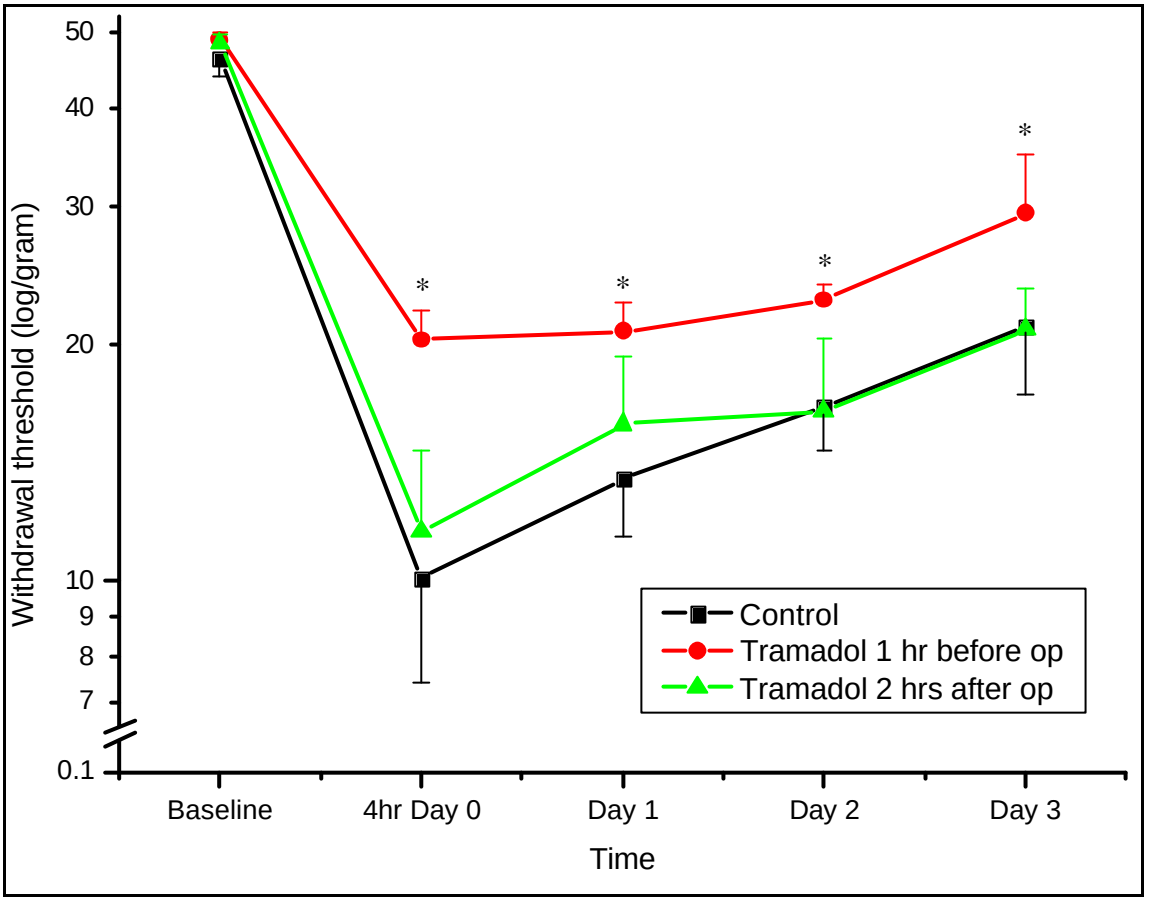

Figure 2.3E Effects of tramadol (40mg/kg), given 1 hr before operation and 2 hrs after operation, on the paw withdrawal threshold in response to mechanical stimuli in rats. The withdrawal threshold of animals treated 1 hr before operation was significantly higher than that of the control group at all observation time points (P = 0.001 for 4 hr Day 0 and Day1, P =0.007 for Day 2 and P = 0.014 for Day 3). Significant difference was found between the before and after operation group at all observation time points with P = 0.001, 0.024, 0.005 and 0.012 respectively.

** $P < 0.05$ for before operation vs. all groups*

The results from Figure 2.3A- 2.3E were then re-organized, according to the time of drug administered into preoperative group and postoperative group, with the control group remaining unchanged as shown in Figure 2.4A and B. Etoricoxib and tramadol, administered 1 hr before incision, produced responses that are significantly different from the control group at all time-points. Although the differences are not statistically significant, etoricoxib exhibited a slight edge over all the tested drugs as shown in the figures. However, this superiority was not found when the drugs were administered 2 hrs after incision as shown in Figure 2.4B.

When the five drugs were re-classified into three pharmacological classes, cox-2 inhibitors (coxibs), non-steroid anti-inflammatory drug (NSAID) and tramadol, differences were noted between the control group and each of the classes. No superiority among the classes was observed (Figure 2.5).

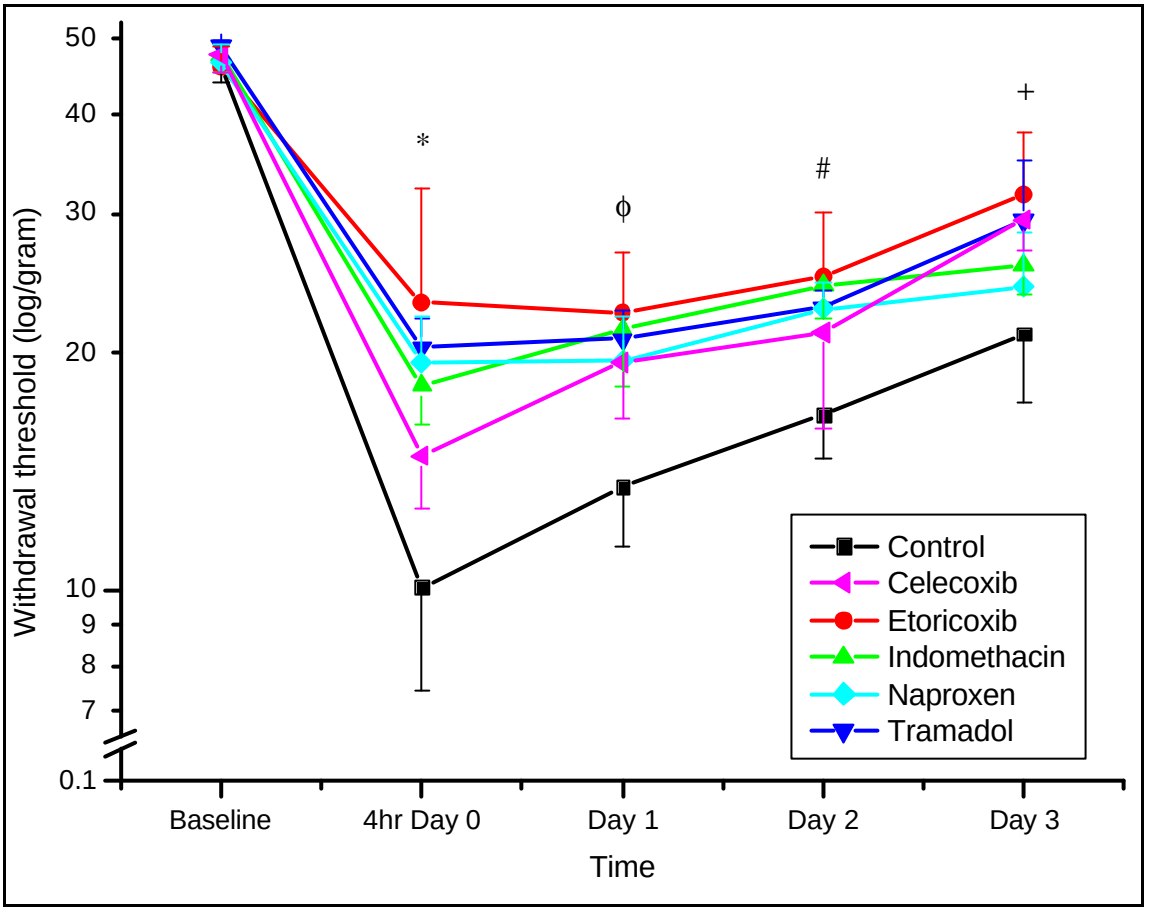

Figure 2.4A Effects of preoperative administration of five different drugs on the paw withdrawal threshold in response to mechanical stimuli in rats. Celecoxib (30mg/kg), etoricoxib (30mg/kg), indomethacin (30mg/kg), naproxen (30mg/kg) and tramadol (40mg/kg) were administered to respective animals 1 hr before incision. At 4 hr Day 0, significant differences were found between the control group and etoricoxib (P = 0.001), indomethacin (P =0.031), naproxen (P = 0.008) and tramadol group (P = 0.005) and between celecoxib and etoricoxib (P = 0.049). Significant differences were found between the control and all other groups at Day 1, with P = 0.026, 0.001, 0.001, 0.023 and 0.005 for celecoxib, etoricoxib, indomethacin, naproxen and tramadol respectively. At Day 2, significant differences were found between the control and etoricoxib (P = 0.005) and indomethacin group (P = 0.006). At Day 3, significant differences were found between the control group and celecoxib (P = 0.028), etoricoxib (P = 0.005) and tramadol group (P = 0.047).

** $P < 0.05$ for control vs. etoricoxib, indomethacin, naproxen and tramadol; and Etoricoxib vs. Celecoxib*
ƒ $P < 0.05$ for control vs. all groups
 # $P < 0.05$ for control vs. etoricoxib, indomethacin, naproxen and tramadol
+ $P < 0.05$ for control vs. celecoxib, etoricoxib and tramadol

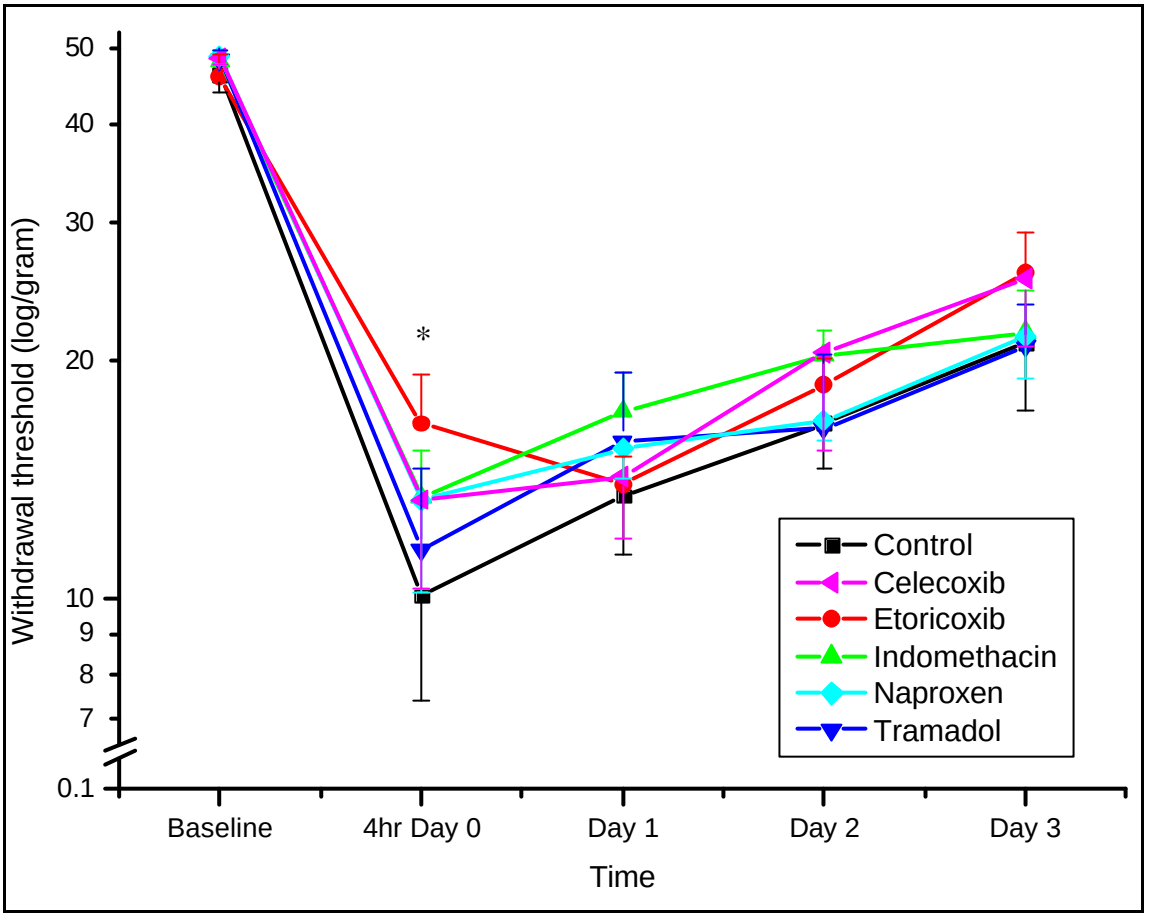

Figure 2.4B Effects of postoperative administration of five different drugs on the paw withdrawal threshold in response to mechanical stimuli in rats. Celecoxib (30mg/kg), etoricoxib (30mg/kg), indomethacin (30mg/kg), naproxen (30mg/kg) and tramadol (40mg/kg) were administered to respective animals 2 hrs after incision. Significant differences were found at 4 hr Day1 between the control and etoricoxib group (P = 0.004), and between the etoricoxib and tramadol group (P = 0.05).

**P < 0.05 for Etoricoxib vs. control and Tramadol*

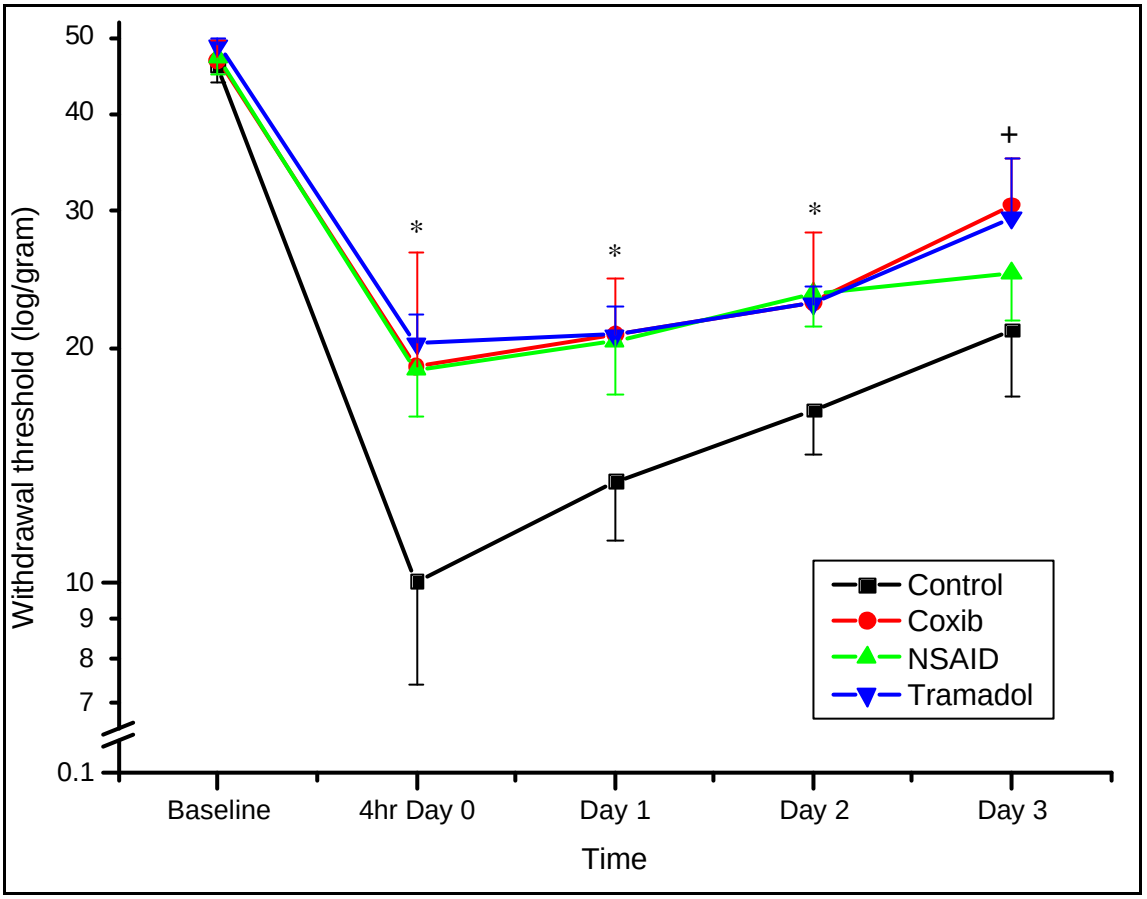

Figure 2.5 Effects of drug classes (coxibs, NSAID and Tramadol), when given preoperatively, on the paw withdrawal threshold in response to mechanical stimuli in rats. The withdrawal threshold produced by both coxibs and tramadol was significantly higher than that of the control group at all observation time points (*P* = 0.006, 0.001, 0.007 and 0.001 for control vs. coxibs at 4 hr Day 0, Day 1, Day 2 and Day 3 respectively; and *P* = 0.007, 0.003, 0.036 and 0.016 for tramadol). Significant difference was found between control and NSAID group at all observation time points except Day 3 (*P* = 0.005, 0.001 and 0.002 for 4 hr Day 0, Day 1 and Day 2 respectively). Significant difference was also found between the coxibs and NSAID group at Day 3 only (*P* = 0.022).

** P < 0.05 for control vs. all groups*
+ P < 0.05 for control vs. coxibs, Tramadol, and for coxibs vs. NSAID

Figure 2.6A- 2.6E shows the cumulative pain scores of the rats administered the respective drugs over a time course of 3 days after the operation. The highest pain score was found at 4 hr after the operation, and decreased over the rest of the observation period. The comparisons between control, pre- and postoperative groups are shown in the figures. Throughout the experimental period, most of the animals remained well groomed and appeared to maintain normal body weight; gait appeared unaffected except for impaired weight bearing on the area of the incision on the first two days after surgery. However, those receiving indomethacin, both pre- and postoperatively, were suffering from mild diarrhea which persisted till Day 3. This might have been due to the gastrointestinal side-effect of conventional non-selective NSAIDs which caused about 5-10% decrease in body weight, which is reflected by higher cumulative pain score on Day 3.

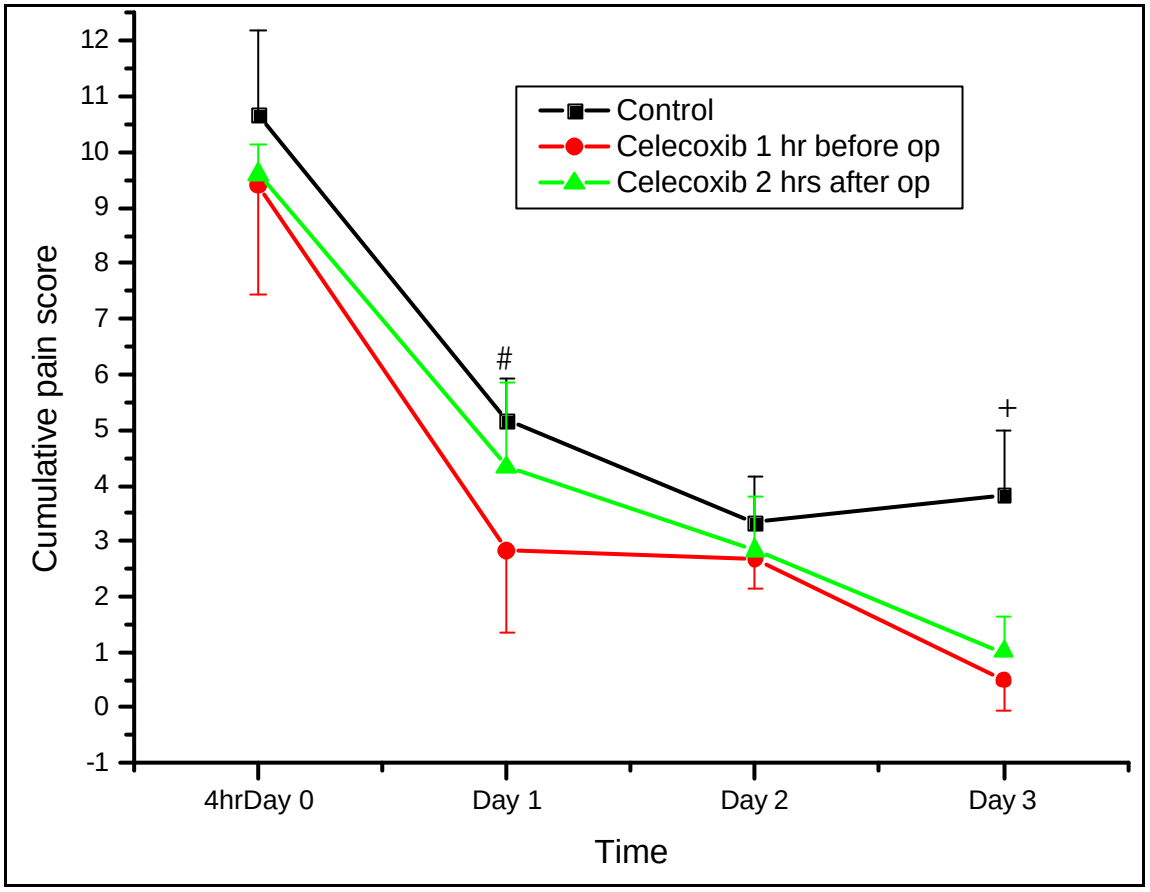

Figure 2.6A Cumulative pain scores of celecoxib (30mg/kg) given 1 hr before operation and 2 hrs after operation. The cumulative pain score for the 1 hr before operation group was significantly lower than that of the control group at Day 1 (P = 0.021) and Day 3 (P = 0.001). Significant difference was found between the control and after operation group at Day 3 with P = 0.001. No significant difference was found between preoperation and postoperation group.

 # $P < 0.05$ for control vs. before operation
+ $P < 0.05$ for control vs. all groups

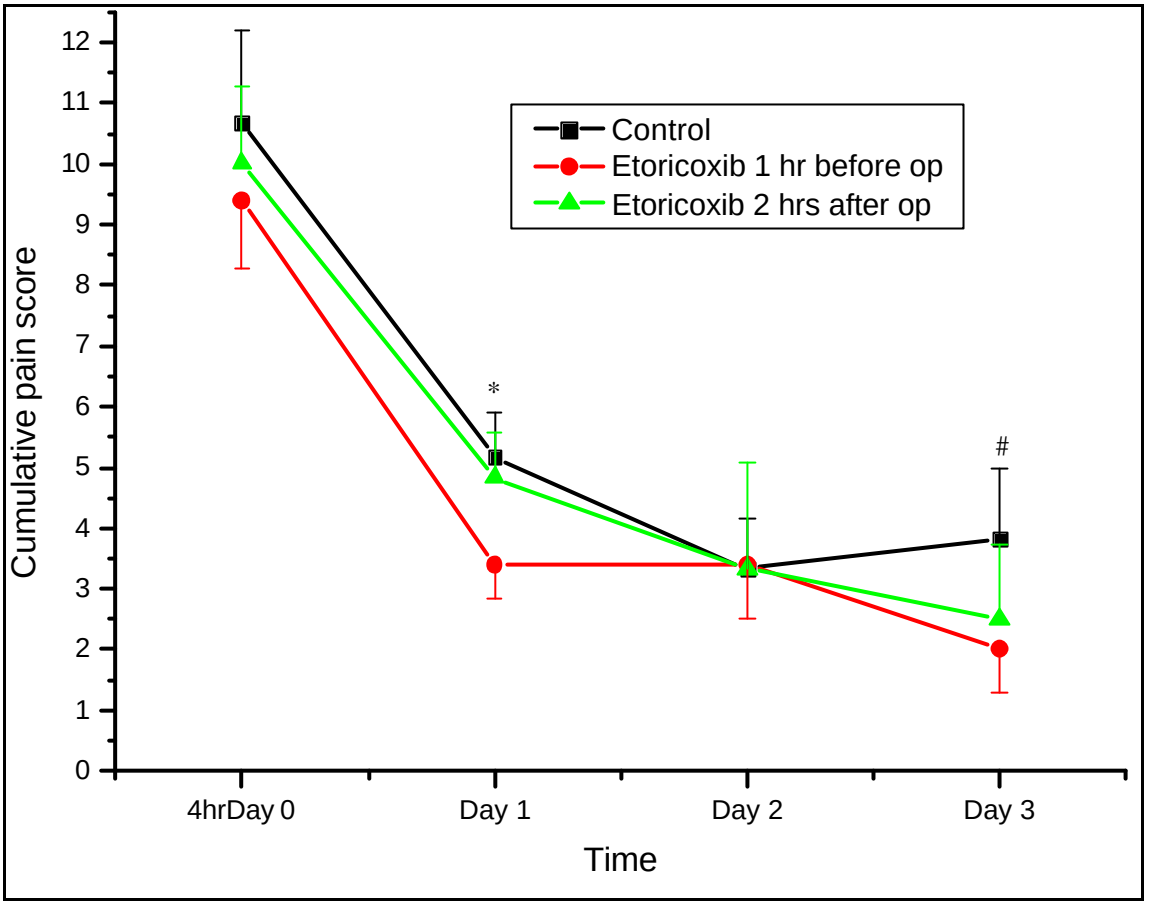

Figure 2.6B Cumulative pain scores of etoricoxib (30mg/kg) given 1 hr before operation and 2 hrs after operation. The cumulative pain score for the 1 hr before operation group was significantly lower than that of the control group at Day 1 (P = 0.003) and Day 3 (P = 0.042). Significant difference was found between the before and after operation group at Day 1 with P = 0.013. No significant difference was found between groups at 4 hr Day 0 and at Day 2.

** $P < 0.05$ for before operation vs. all groups*
 # $P < 0.05$ for control vs. before operation

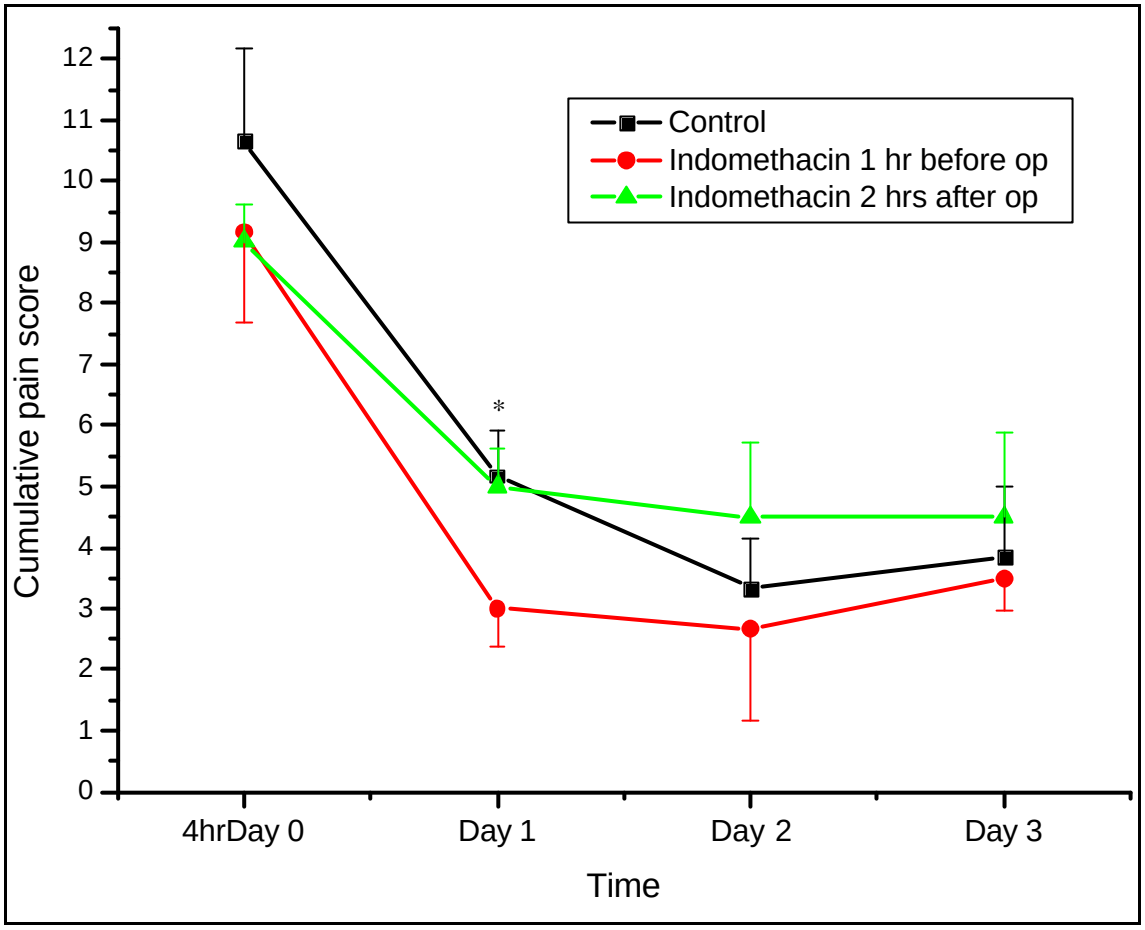

Figure 2.6C Cumulative pain scores of indomethacin (30mg/kg) given 1 hr before operation and 2 hrs after operation. The cumulative pain score for the 1 hr before operation group was significantly lower than that of the control group at Day 1 (P = 0.001). Significant difference was found between the before and after operation group at Day 1 with P = 0.001. No significant difference was found between groups at other observation time point.

** $P < 0.05$ for before operation vs. all groups*

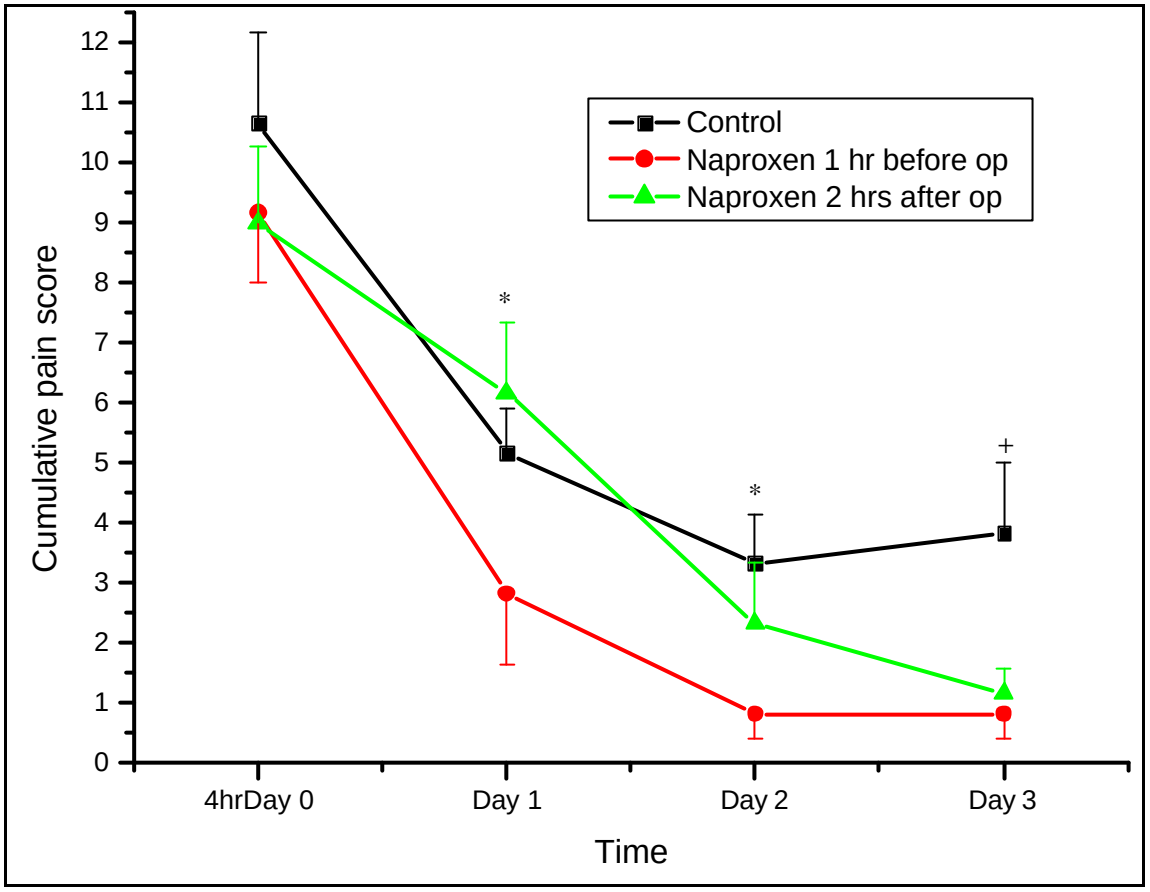

Figure 2.6D Cumulative pain scores of naproxen (30mg/kg) given 1 hr before operation and 2 hrs after operation. The cumulative pain score for the 1 hr before operation group was significantly lower than that of the control group at Day 1, Day 2 and Day 3 (P = 0.005, 0.001 and 0.001 respectively). Significant difference was found between the before and after operation group at Day 1 with P = 0.001 and Day 2 with P = 0.016. Significant difference was also found between the control and after operation group at Day 3 (P = 0.001).

** $P < 0.05$ for before operation vs. all groups*
+ $P < 0.05$ for control vs. all groups

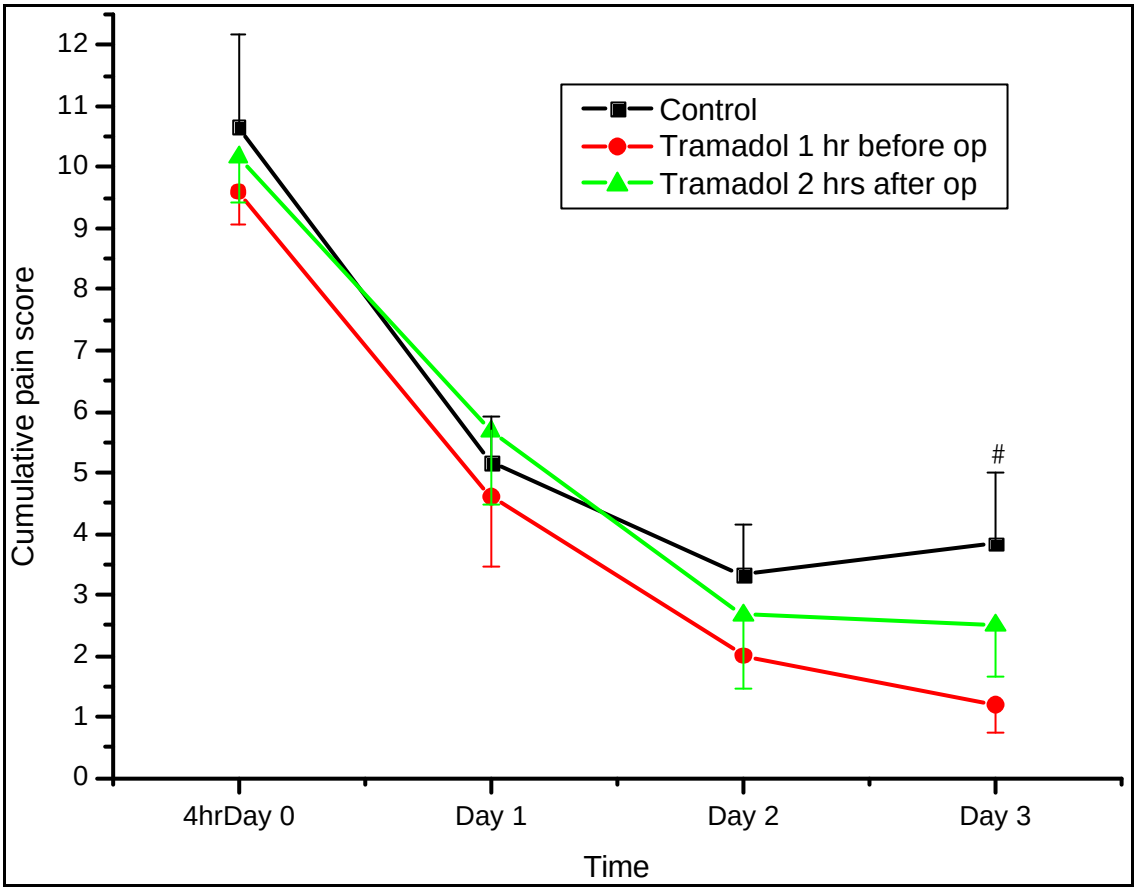

Figure 2.6E Cumulative pain scores of tramadol (40mg/kg) given 1 hr before operation and 2 hrs after operation. The cumulative pain score for the 1 hr before operation group was significantly lower than that of the control group at Day 3 with *P*= 0.001. No significant difference was found between groups at any other observation time point.

 # P < 0.05 for control vs. before operation

2.3.2 Effects of time and dose of administration

Figure 2.7 summarizes the time effectiveness of 30 mg/kg etoricoxib, administered at different time-points before the operation (1 hr, 12 hrs, 1 day and 2 days before operation). None of the group exhibited superiority. Differences were only found between the control group and the 1 hr or 12 hrs groups. When the drug was given 1 hr before incision, the threshold was significantly higher than that of control group at all time-points. When it was given 12 hrs before incision, the threshold was significantly higher than that of control group at Days 1, 2 and 3.

Figure 2.8 shows the withdrawal thresholds of different doses of etoricoxib (10, 20 and 30 mg/kg) when given 1 hr before the operation. These three groups showed no statistical significant difference. However, when compared with the control group, the thresholds of 20 mg/kg and 30 mg/kg groups showed a similar trend and are significantly different from that of control group (except 30 mg/kg at Day 2). The withdrawal threshold of animals treated with etoricoxib 30mg/kg was significantly higher than that of the control group at all observation time points except at Day 2 (P = 0.004, 0.005, 0.008 for 4 hr Day 0, Day 1 and Day 3, respectively). The withdrawal threshold of animals treated with etoricoxib 20mg/kg was significantly higher than that of the control group at all observation time points (P = 0.034, 0.003, 0.044, 0.049 for 4 hr Day 0, Day 1, Day 2 and Day 3, respectively).

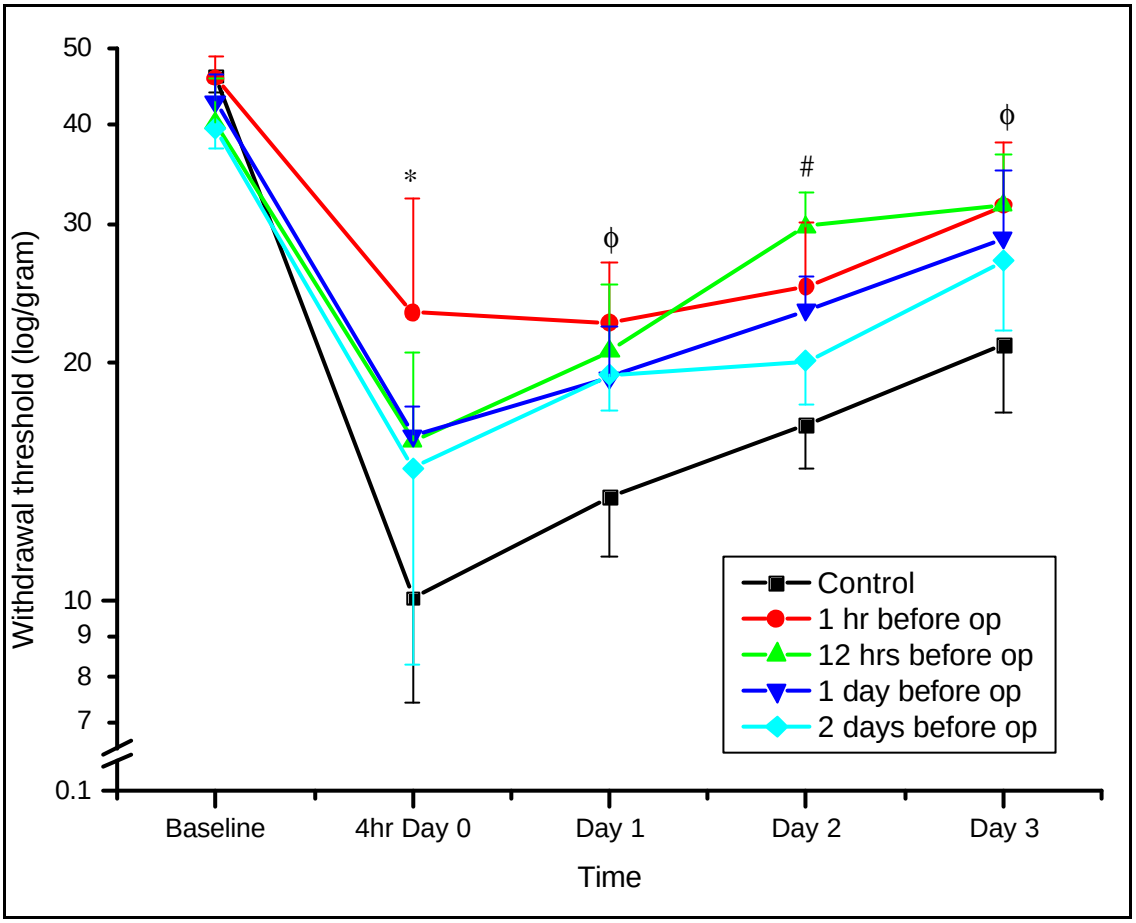

Figure 2.7 Withdrawal thresholds when 30 mg/kg etoricoxib was given at different time points preoperatively. The withdrawal threshold of animals treated 1 hr before operation was significantly higher than that of the control group at all observation time points (P = 0.006, 0.002, 0.003 and 0.035 for 4 hr Day 0, Day 1, Day 2 and Day 3 respectively). Significant difference was found between the control and 12 hrs before operation group at Day 1 (P = 0.015), Day 2 (P = 0.001) and Day 3 (P = 0.033). At Day 2, significant difference was also found between the control and 1 day before operation group, P = 0.014; between the 12 hrs and 1 day before operation group, P = 0.028; and between the 12 hrs and 2 days before operation group, P = 0.001.

** $P < 0.05$ for control vs.* 1 hr group
ƒ $P < 0.05$ for control vs. 12 hr and 1 hr group
 # $P < 0.05$ for control vs. 12 hr, 1 hr, 1 Day group; and for 12 hr vs. 1 Day and 2 Days group.

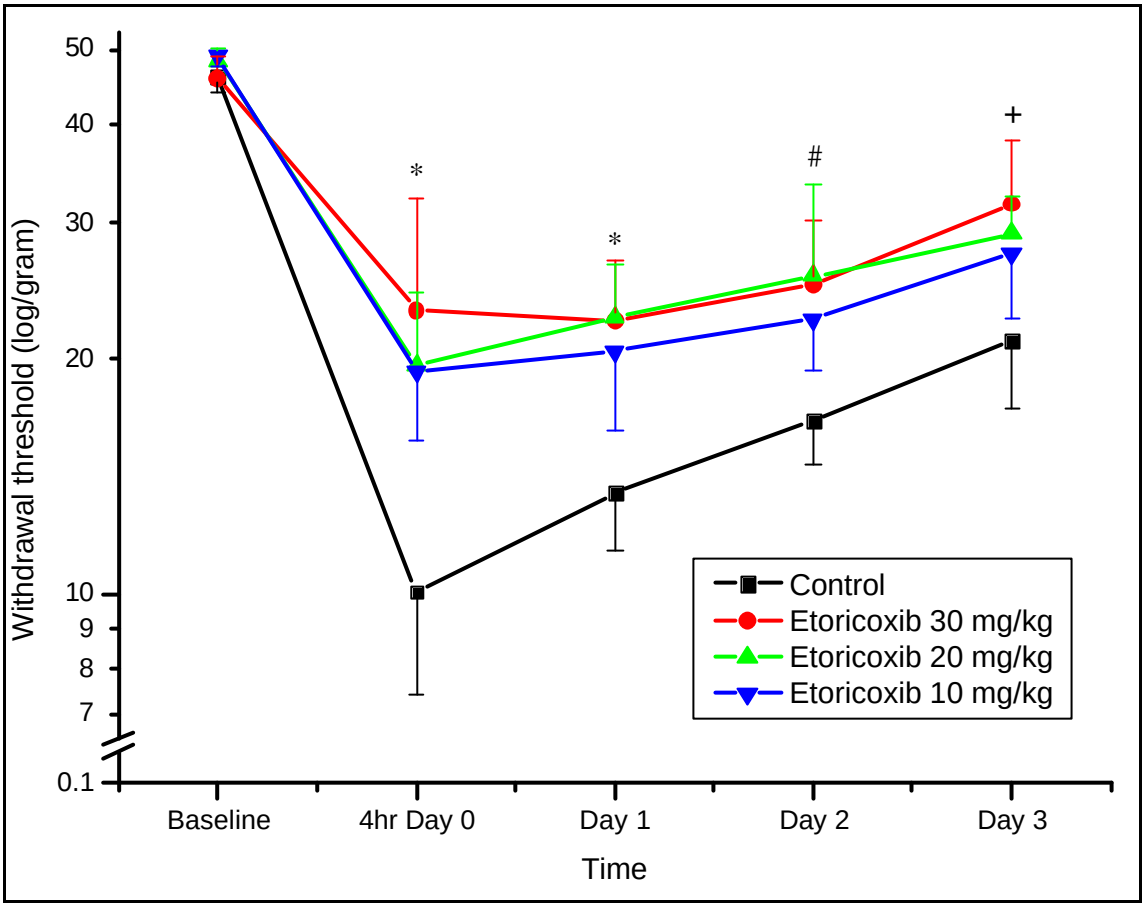

Figure 2.8 Withdrawal thresholds when different doses of etoricoxib (30mg/kg, 20mg/kg and 10mg/kg) were given 1 hr before surgery. The withdrawal threshold of animals treated with etoricoxib 30mg/kg was significantly higher than that of the control group at all observation time points except at Day 2 (P = 0.004, 0.005, 0.008 for 4 hr Day 0, Day 1 and Day 3 respectively). The withdrawal threshold of animals treated with etoricoxib 20mg/kg was significantly higher than that of the control group at all observation time points (P = 0.034, 0.003, 0.044, 0.049 for 4 hr Day 0, Day 1, Day 2 and Day 3 respectively).Significant difference was found between the control and etoricoxib 10mg/kg group at 4 hr Day 0 (P = 0.045) and Day 1(P = 0.026). No significant difference was found between different doses group at any observation time point.

** P<0.05 for control vs. all groups*
 # P<0.05 for control vs. 20 mg/kg group
+ P<0.05 for control vs. 30 mg/kg and 20mg/kg group.

2.4 Discussion

In this study, the preemptive analgesic effects of celecoxib, etoricoxib, indomethacin, naproxen and tramadol were evaluated in a rat model of incisional pain. It was done by comparing the withdrawal thresholds and cumulative pain scores between the groups, namely, the control, preoperative and postoperative groups which were administered with different drugs.

The findings indicate that, preoperative administrations of the five drugs exhibited significantly higher withdrawal thresholds than that of placebo control group for 3 days after surgery. Preoperative administration of etoricoxib, indomethacin, naproxen and tramadol produced an effect which was significantly higher when compared with that of postoperative administration for up to 2 days after the surgery (please refer to respective figures for *P* value). These findings suggest that the four drugs exhibit better analgesic effect when given preoperatively, which supports the idea of preemptive analgesia. Taking tramadol as a typical example, Figure 2.3E shows that preoperative administration of tramadol exhibited a significant difference in withdrawal threshold when compared with both postoperative tramadol and the control group at all observation time-points. The withdrawal threshold of animals treated 1 hr preoperatively was significantly higher than that of the control group at all observation time points ($P = 0.001$ for 4 hr Day 0 and Day1, $P = 0.007$ for Day 2 and $P = 0.014$ for Day 3). Significant difference was found between the before and after operation group at all observation time points with $P = 0.001$, 0.024, 0.005 and 0.012, respectively. Moreover, no significant difference was found between the responses in

the postoperative and control groups. These may suggest that tramadol exerts better analgesic effect when administered preoperatively than postoperatively. This finding, however, has not been fully supported by clinical studies focused on preemptive analgesic effect of tramadol, and the published results are conflicting [69-71].

Whiteside et al., [65] had reported in their study that the antinociceptive effects of several analgesics are dose-dependent with the greatest effects being observed at the highest doses. In our study, although the dose-dependent property is not obvious, however an adequate dose was needed in order to obtain good preemptive analgesic effect. At the lower dose, etoricoxib 10 mg/kg in our case, showed an improvement over the control group, the difference is not significant. There is a risk of masking of the preemptive analgesic properties of a potential drug if sub-optimal dose is used. The doses of drugs used in this study were selected from those used in other studies [65-68], but none of them had been applied for evaluation of the preemptive analgesic effects in this model. Celecoxib 30 mg/kg in our study yielded a less preemptive analgesic effect compared with other drugs. This result should not be interpreted absolutely, as further studies should be conducted using higher doses of celecoxib before a conclusion can be drawn.

In our study, single-dose regimen was used in both pre- and postoperative settings. It is noted that a single dose of drug, when administered 1 hr preoperatively, produced an effect that lasted for 2 or 3 days postoperatively. This finding further supports the idea of preemptive analgesia which prevents the establishment of central sensitization caused by incisional and inflammatory injuries and covers the period of surgery and

the initial postoperative period. Further study may involve multi-dosing regimens which extend into the recovery period to further control the postoperative pain.

In this study, we compared the withdrawal threshold produced by 30mg/kg etoricoxib given at different time points preoperatively (1hr, 12 hrs, 1 day and 2 days before operation). According to Figure 2.7, the withdrawal thresholds of animals treated 1 hr and 12 hrs before operation were significantly higher than that of the control group at all observation time points (except 4 hr Day 0 for 12 hrs before operation group). However, these four groups did not show any superiority when compared among each other. Significant difference was only found at Day 2 between 12 hrs and 1 day before operation group ($P = 0.028$) and between 12 hrs and 2 days before operation group ($P = 0.001$). No other significant difference in preemptive analgesic effectiveness for etoricoxib administered 1 hr, 12 hr, 1 day and 2 days before incision was observed. Thus, the timing of drug administration is unlikely to be a prerequisite for preemptive analgesia, which is consistent with another study [72]. Nevertheless, the basic pharmacokinetic parameters such as half-life ($t_{1/2}$) and time to the maximum concentration (t_{max}) must be taken into consideration when choosing a suitable candidate and planning a relevant study.

Pain in animals is difficult to assess. Besides the withdrawal responses to mechanical stimuli, a numerical pain scoring scale has been developed in this study to further assess the pain status in rats. The scale was developed by adapting from several measures that had been used in other studies [62-64], which was then customized to fit into our protocol. The results showed that the pain scores of preoperative group are

generally lower than that of control group, which is consistent with the result of the withdrawal responses. However, when comparing the pain score between pre- and postoperative group, the significant difference was only found in four points, at Day 1 in the etoricoxib group ($P = 0.013$), at Day 1 in the indomethacin group ($P = 0.001$), at Day 1 and Day 2 in naproxen group ($P = 0.001$ and 0.016). The result is too minute to permit a conclusion. Some limitation has been noted. The scale used here has not been validated in any other situation, and in fact there is a general lack of validated scales available. The parameter used in this scale depends on the clinical appearance of the rats which is always subjective and varies considerably. The signs of pain may be very subtle, and some of it may only be noticeable at night. Thus, it strongly depends on the experience of the observer who should be familiar with the normal and abnormal behaviors of rats. Despite these limitations, it provides a means for close observation of animal well-being, any harmful abnormality can be identified and decision can then be made to discontinue the protocol and the animal be sacrificed accordingly.

Moderate to severe peri-operative pain has traditionally been managed using opioid-analgesics, with morphine being the standard reference drug, because of its known potency and fast onset of action. However, concerns regarding opioid-related side-effects (e.g. CNS depression and sedation, respiratory depression, nausea, vomiting, urinary retention, constipation, tolerance and the potential for abuse by health care professionals) limit the use of opioids despite their analgesic efficacies in postoperative analgesia; and have stimulated a search for powerful non-opioid analgesics [73, 74]. Non-steroidal anti-inflammatory drugs (NSAIDs, e.g. indomethacin

and naproxen), cyclooxygenase-2 inhibitors (coxibs, e.g. celecoxib and etoricoxib) and tramadol, which act through different pathways, may be used to fill this need. Conventional nonselective NSAIDs have well recognized adverse effects (e.g. interference in platelet aggregation, homeostasis and irritation of gastric mucosa) that are contraindications in the preoperative setting, making coxibs (selective Cox-2 inhibitors) and tramadol (centrally acting, synthetic opioid analgesia) better choices as preemptive analgesia.

The finding of this study is encouraging, and may arouse the interest of further research on the preemptive analgesia. Future studies on the combination of preemptive analgesia and multimodal analgesic strategy, multi-dose regimen trials and randomized controlled clinical trials will be needed to confirm the clinical relevance of preemptive analgesia.

Chapter III – Clinical study: Analgesic efficacy of tramadol and rofecoxib in Asian haemorrhoidectomy patients

3.1 Hypothesis

Pain control following surgery remains an important aspect of patient care in the ambulatory setting and this is true for the postoperative haemorrhoidectomy patient [75]. Currently, there is no published study comparing the analgesic efficacies of tramadol and rofecoxib in patients undergoing haemorrhoidectomy. Rofecoxib, with its anti-inflammatory property and longer elimination half-life (12 hrs vs. 6 hrs), may make a better analgesic than tramadol when administered preoperatively. We hypothesized that rofecoxib administered 1 hr preoperatively would give better pain control and side effect profile than that of tramadol. The aim of this study was to compare the analgesic efficacies and safety profiles of tramadol and rofecoxib in Asian patients undergoing haemorrhoidectomy.

3.2 Materials and Methods

3.2.1 Clinical setting and subjects

The study was conducted at Singapore General Hospital (SGH) with approval from the hospital's ethics committee and all participants signed the informed consent forms. Patients who were scheduled to undergo haemorrhoidectomy at SGH, who were at least 21 years of age, able to take oral medication and able to communicate meaningfully, were considered for recruitment in the study. Patients were excluded if they had a known hypersensitivity to tramadol or rofecoxib or other NSAIDs, with a

history of seizure disorder, epilepsy or other neurological impairment, with suspected abuse of narcotics or alcohol, are pregnant or lactating, with impaired renal or liver function, are undergoing concurrent treatment with monoamine oxidase inhibitors (MAOIs) or analgesic agents, with severe terminal illness, with a history of peptic ulcer disease, gastrointestinal bleeding or perforation or severe congestive heart failure.

This was a single-blind study, only the investigators were aware of which intervention each patient is receiving. Patients undergoing haemorrhoidectomy were assigned randomly using computer generated random numbers to receive either one of two treatments: tramadol hydrochloride (Tramadol 50 Stada®; STADApharm) 100 mg preoperatively and subsequently 50 mg three times daily when required for pain, or rofecoxib (Vioxx™; MSD) 50 mg preoperatively and subsequently 50 mg once a day when required for pain. Preoperative dose was administered no less than 1 hour before operation with a measured amount of 20 ml of water.

After surgery, patients were transferred to the recovery area where they were monitored by the anesthetists and nurses before being discharged to their respective wards. In case of inadequate pain relief at the recovery area, rescue analgesia was provided by titrated doses of morphine in accordance with hospital policy. Patients were advised to take the study medication as directed when they were discharged from the hospital. If the study medication was inadequate for pain relief 1 hour after administration, patients were instructed to take oral rescue medication, which was two 500 mg tablets of paracetamol, up to a maximum of 8 tablets a day.

All operations were performed under general anesthesia. The anesthetic regimes were standard to the local hospital practice. Induction and maintenance anesthetic agents were given at the discretion of the attending anesthetist.

3.2.2 Pain and postoperative measures

Pain scores were obtained from the patients at the time the preoperation analgesic dose was administered, and at 0.5, 1, 1.5, 2, 3, 4 hours after surgery. Pain scores were also obtained at time of discharge and daily for 3 days after the day of the surgery using telephone contact. Pain assessment was conducted using the Numerical Rating Scale (NRS, Appendix II) and Verbal Rating Scale (VRS, Appendix III). The NRS consists of a series of numbers ranging from 0 to 10 with end-points being labeled with 'no pain' and 'worst possible pain', respectively. The VRS is a list of adjectives describing the different levels of pain intensity on a 5-point scale, which was scored as follows: no pain (0); no pain at rest, slight pain on movement (1), slight pain at rest, moderate pain on movement (2); moderate pain at rest, severe pain on movement (3), severe pain at rest, and on movement (4). Patients were asked to rate their pain according to the number or adjectives that best corresponded to their pain. The consumption of rescue medication was noted from the patient medication record and patient's recall during the follow-up telephone interview.

Side effects were recorded based on those observed by the investigator or based on patient's responses. Safety of the study medications was evaluated based on the

incidence of side effects experienced by the patients in the inpatient setting and after discharge.

Both the English versions of the NRS and VRS were translated into Chinese and Malay. All interviews and explanation of the protocol were conducted in either English, Chinese and Malay language according to patient's preference.

3.2.3 Statistical analysis

Computer software SPSS 11.0 for windows was employed in all statistic tests. Significance was tested by unpaired two-tailed student's *t* test or Fisher's Exact test where appropriate. In all cases, a p-value < 0.05 was considered statistically significant.

3.3 Results

Twenty-five patients completed the study with 11 patients in the tramadol group and 14 in the rofecoxib group. Demographic data concerning the patient's age, gender, race, method of haemorrhoidectomy and baseline (preoperative) pain scores were shown in Table 3.1. There were no significant differences between two treatment groups in all demographic variables.

Table 3.1 Demographic Data, by treatment group.

Variable	**Tramadol (n = 11)**	**Rofecoxib (n = 14)**
Age (mean ± SD)	43.18 ± 8.750	36.50 ± 10.733
Gender (No., %)		
Male	5 (45.5%)	10 (71.4%)
Female	6 (54.5%)	4 (28.6)
Race (No., %)		
Chinese	10 (90.9%)	11 (78.6%)
Malay	1 (9.1%)	3 (21.4%)
Method of haemorrhoidectomy (No., %)		
Conventional	9 (81.8%)	6 (42.9%)
Stapled	2 (18.2%)	8 (57.1%)
Baseline pain score (NRS, mean ± SD)	0.36 ± 1.206	0.5 ± 1.160

SD = Standard Deviation, NRS = Numerical Rating Scale

The mean NRS and VRS pain scores obtained at 11 assessment time-points over a 4-day study period were shown in Figure 3.1A and 3.1B. The tramadol group had lower NRS pain scores preoperatively and at 0.5, 1 and 4 hours postoperatively, and the rofecoxib group had lower pain scores for the rest of the time. The distribution of VRS pain scores was similar to that of the NRS; the tramadol group had lower VRS pain scores preoperatively and at 0.5 and 1 hour postoperatively, whereas the rofecoxib group showed lower pain scores at other assessment points. However, the differences between groups were not statistically significant at any of the assessment time-points for both NRS and VRS pain scores, with exception at Day 3.

At day 3 after the surgery, 90% of patients described their feelings with either 'no pain' or 'no pain at rest, slight pain on movement'. Only one patient (from tramadol group and underwent conventional haemorrhoidectomy) described her feeling as 'moderate pain at rest, severe pain on movement' and rated the NRS as 9. This patient complained that her wound was swollen and inflamed; she was then referred back to hospital.

The number of study medication taken postoperatively was monitored through the follow-up telephone interview. Rofecoxib was required by all patients for 3 days postoperatively except 1 patient who did not need any analgesic for the second and third day postoperatively. Tramadol was required by most of the patients for 3 days postoperatively except 2 patients. One of them refused to take any analgesic for pain relief even though she still felt some pain after discharge from hospital. This patient was then advised to take medication for pain relief according to the prescription.

Another patient did not need any analgesic for the third day after operation. There were 2 and 4 patients in the tramadol and the rofecoxib groups, respectively, (18.2% vs. 28.6%, $p > 0.1$) who needed rescue medicine because of insufficient pain relief. One of the patients in the tramadol group was given pethidine intravenously at the recovery unit, and required oral paracetamol later on. The other patient in the tramadol group took paracetamol as rescue medicine. Only one patient in the rofecoxib group needed extra morphine intravenously as rescue medicine at the recovery unit while another three required oral paracetamol at home. One of them revealed that he took paracetamol for fever on Day 3 after the operation but not for pain relief.

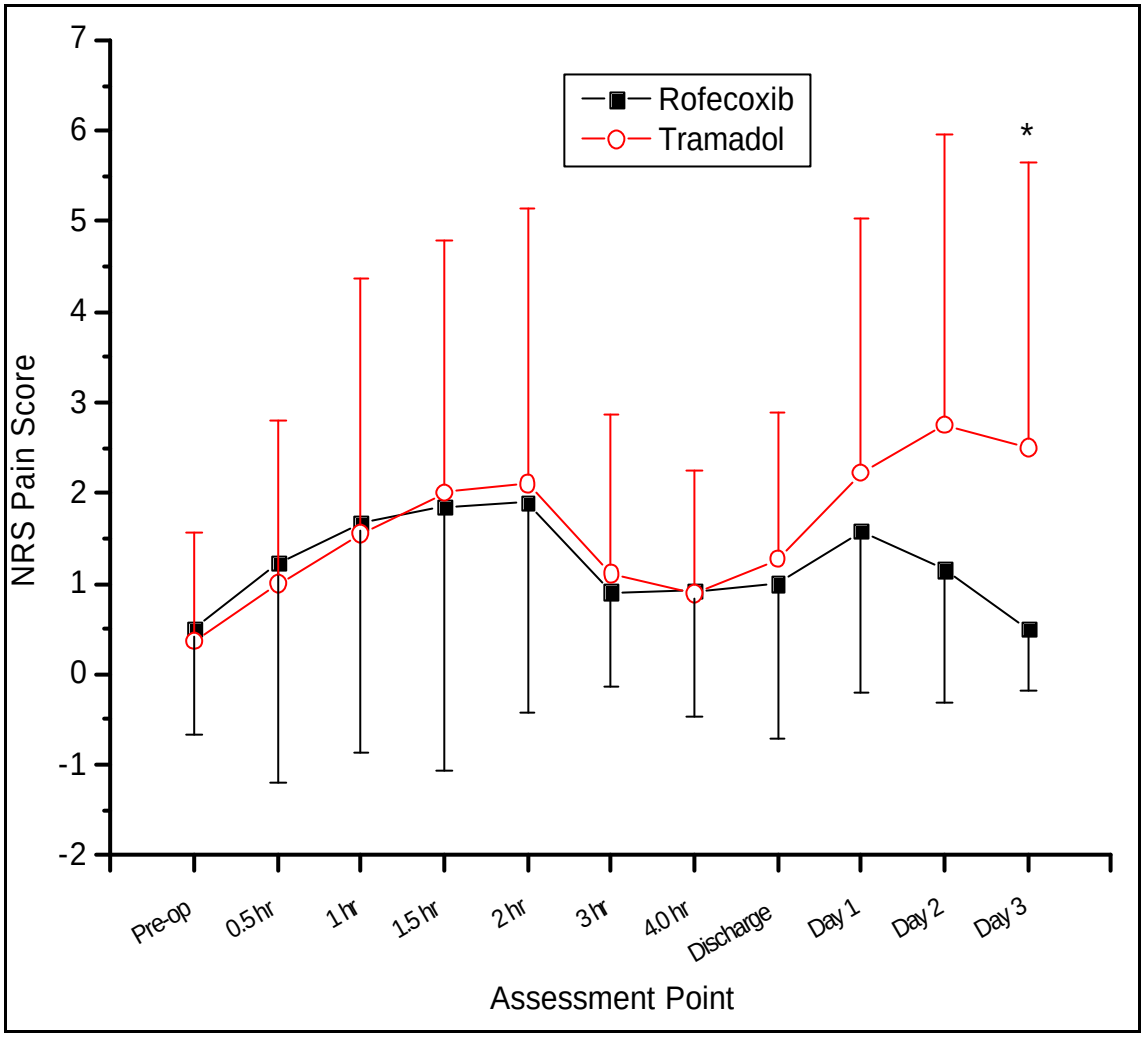

Figure 3.1A Time-effect curve for mean Numerical Rating Scale (NRS) pain scores for two treatment groups. Significant difference between two treatment groups was detected only at Day 3 (P = 0.046). No significant difference was found at any other observation time point.

** $P < 0.05$*
Discharge: time of discharge

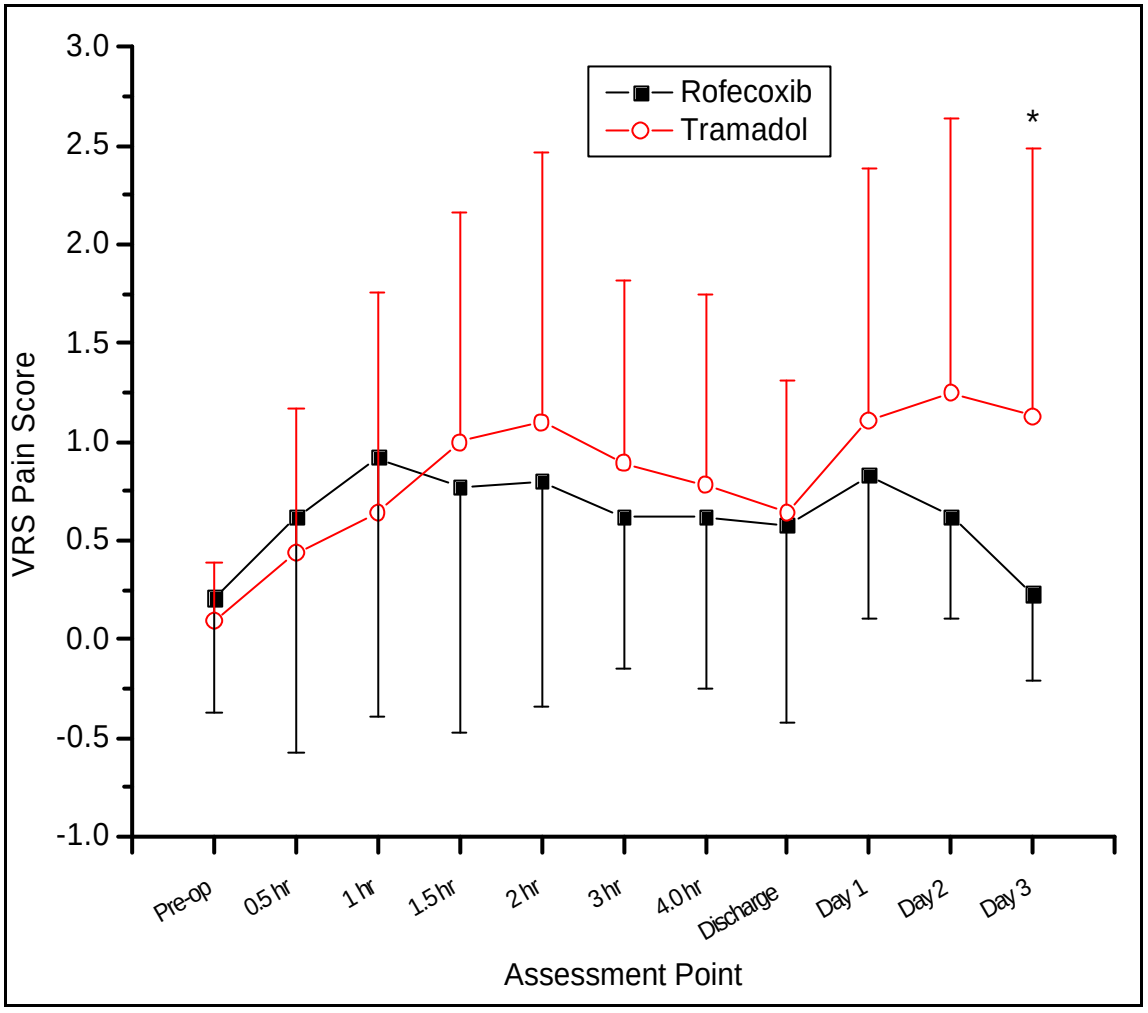

Figure 3.1B Time-effect curve for mean Verbal Rating Scale (VRS) pain scores for two treatment groups. Significant difference between two treatment groups was detected only at Day 3 (P = 0.038). No significant difference was found at any other observation time point.

** $P < 0.05$*
Discharge: time of discharge

The unwanted symptoms presented or reported by patients postoperatively were nausea, nausea with vomiting, dizziness, hypotension, urinary retention, shivering, constipation, bloated and diarrhea. The summary of the incidence of symptoms presented by patients is shown in Table 3.2. The incidence of nausea and dizziness was significantly higher in the tramadol group compared to the rofecoxib group. There were no significant differences in other incidences as shown in Table 3.2. However, it is noted that the tramadol group showed relatively higher incidence of both nausea with vomiting and hypotension compared with the rofecoxib group. More that half (54.5%) of the patients who took tramadol preoperatively showed nausea with vomiting or hypotension (different patients were involved for each episode). The hypotensives needed normal saline infusion to restore their blood pressure at the recovery unit and two patients in the tramadol group needed ondansetron intravenously to control the symptoms. None of them showed either of the symptoms on the first day after surgery.

Table 3.2 Side effects experienced by patients, by treatment group.

Symptom	**Tramadol (n = 11) No. (%)**	**Rofecoxib (n = 14) No. (%)**	***p*-value**
Nausea	7 (63.6%)	3 (21.4%)	< 0.05
Nausea with vomiting	6 (54.5%)	2 (14.3%)	0.081
Dizziness	8 (72.7%)	3 (21.4%)	< 0.05
Hypotension	6 (54.5%)	2 (14.3%)	0.081
Urinary retention	1 (9.1%)	3 (21.4%)	0.604
Shivering	2 (18.2%)	1 (7.1%)	0.565
Constipation	1 (9.1%)	1 (7.1%)	1.000
Bloated (gas in stomach)	0	2 (14.3%)	0.487
Diarrhea	0	1 (7.1%)	1.000

3.4 Discussion

Optimal postoperative pain control should be effective and safe. The analgesic used should produce minimal side effects, facilitate recovery and be easily managed by patients at home [76].

Quantitative assessment of analgesic efficacy is difficult, since pain is inherently subjective in nature, with the severity of pain being affected by emotional factors. Thus, there are currently no objective measures available for assessing pain intensity [46]. In the absence of any truly objective measures, the Verbal Rating Scale (VRS) and Numerical Rating Scale (NRS) have been used effectively in hospital clinics and have provided valuable information about pain and analgesia. In addition, VRS and NRS provide simple, efficient, and minimally intrusive measures of pain intensity and have been used widely in the clinical and research settings where a quick index of pain intensity is required and to which a numerical value can be assigned [77, 78].

As seen in Figures 3.1A and 3.1B, the mean NRS and VRS pain scores obtained during the whole study period were rather similar between two treatment groups. Significant difference was only found at Day 3 after discharge from hospital. It is noted that, one patient (from the tramadol group) rated NRS and VRS as 9 and 4, respectively, for 3 days after discharge, was found with inflamed wound later on. This result has contributed to the significant difference in the NRS and VRS score between two treatment groups with wide standard deviation (SD) (P = 0.046, 0.038; SD = 3.162, 1.356 for NRS and VRS respectively). If this particular result is excluded from the analysis, there will be no significant difference found in the NRS and VRS scores

between two treatment groups with smaller SD (P = 0.09, 0.084; SD= 1.902, 0.756 for NRS and VRS, respectively). The rofecoxib group showed lower pain scores generally, except in the early postoperative period. However, no significant difference was detected at any of the assessment time-points. Although it was not established which treatment is superior, this study suggests that tramadol and rofecoxib showed comparable analgesic effects, which is further supported by similar consumption of rescue medications between the groups. 87% and 90% of patients described their pain at discharge time and at day 3 after surgery as 'no pain' or 'no pain at rest, slight pain on movement'. Three patients revealed that they only felt pain during defecation, suggesting that majority of our patients received sufficient postoperative pain relief. All patients were discharged with a local anesthetic, lignocaine gel, which acts synergistically with the oral analgesic to relieve postoperative pain. This may affect the result to some extent, as pain relief is not solely due to the oral analgesic.

Different methods of surgery may vary the intensity and perception of pain. In this study, either conventional or stapled haemorrhoidectomy was conducted. The method of haemorrhoidectomy used was determined at the discretion of surgeon and was beyond the consideration of this study. There was no difference in the anaesthetics used in both type of operations, which consisted of induction with propofol and maintained with isoflurane, nitrous oxide and oxygen. When the mean VRS and NRS scores of different surgery methods were compared, stapled haemorrhoidectomy had generally lower pain score (with the exception of 0.5 and 1 hour postoperation) compared with those of conventional haemorrhoidectomy (see Figures 3.2A and 3.2B). However, no significant differences were detected at any point during the

whole study period. The surgical methods may play an important role in pain intensity, but it did not significantly affect the results in this study. Nonetheless, there was much smaller number of patients undergoing stapled haemorrhoidectomy (2/11) in the tramadol group compared to rofecoxib group (8/14). Stapled haemorrhoidectomy had generally lower pain scores if compared with that of conventional haemorrhoidectomy, this could contribute to the higher pain scores for tramadol on Day 3, since the number of patients undergoing stapled haemorrhoidectomy was fewer.

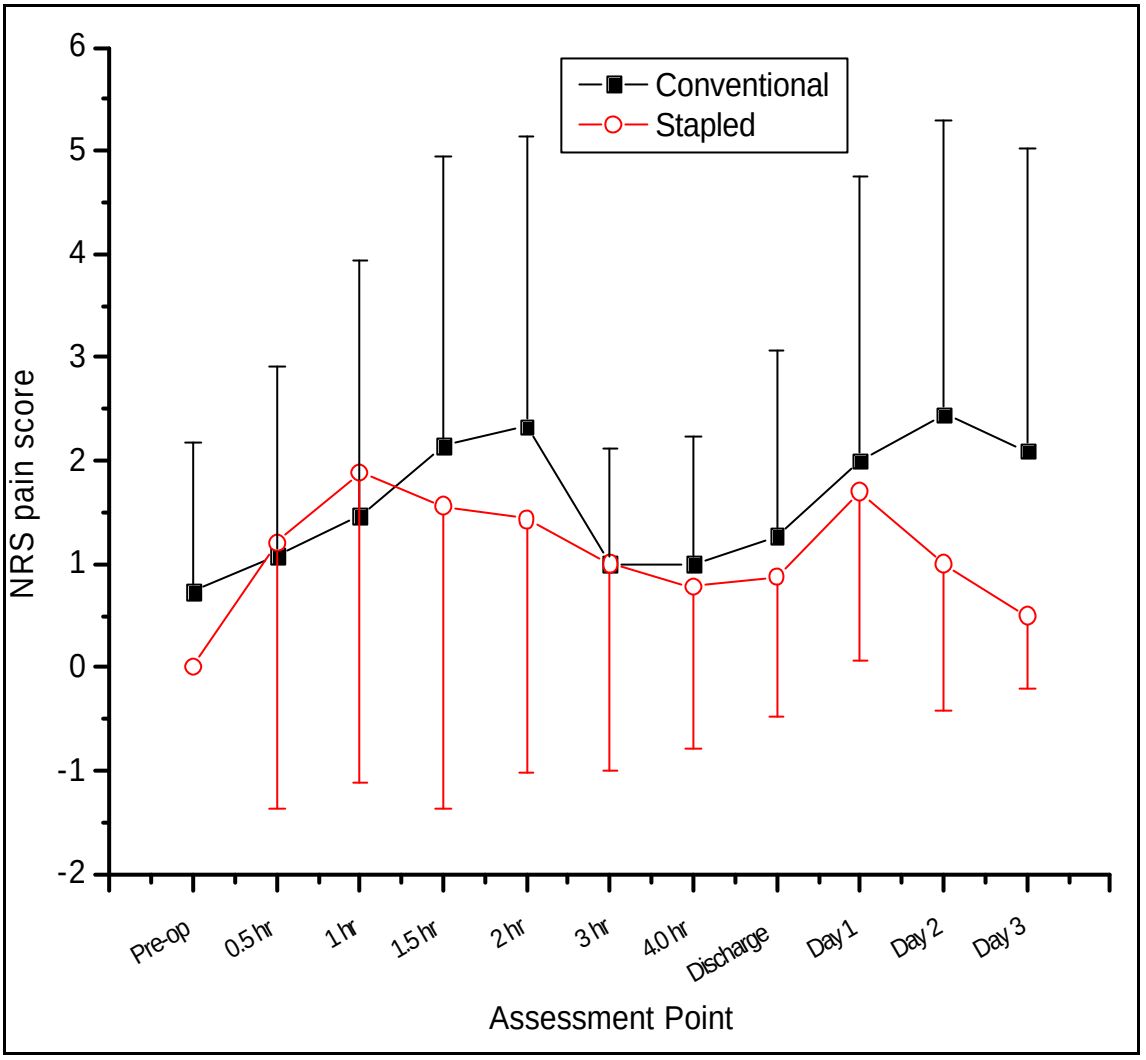

Figure 3.2A Time-effect curve for mean Numerical Rating Scale (NRS) pain scores for different methods of haemorrhoidectomy used. No significant difference was detected at any of the assessment points.

Discharge: time of discharge

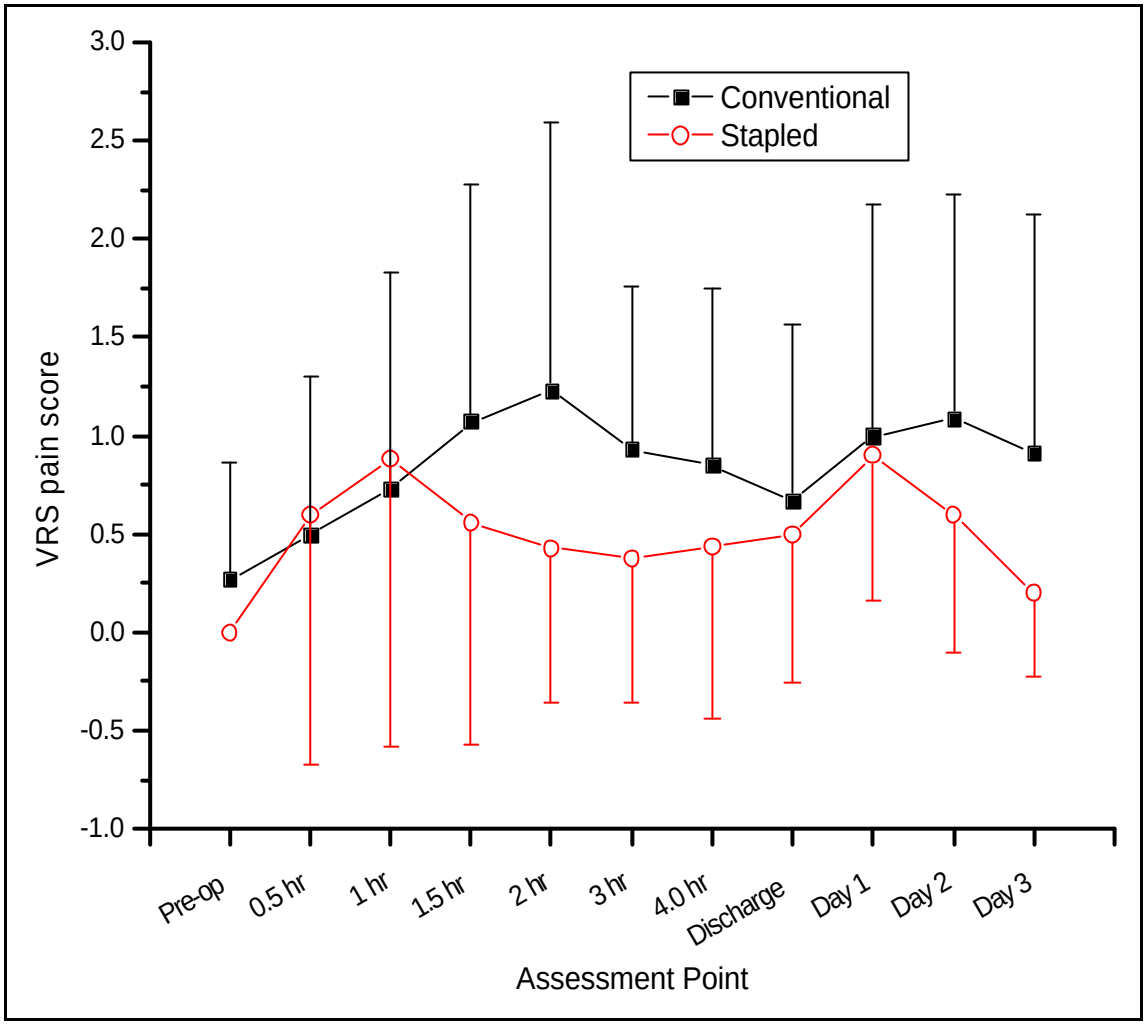

Figure 3.2B Time-effect curve for mean Verbal Rating Scale (VRS) pain scores for different methods of haemorrhoidectomy used. No significant difference was detected at any of the assessment points.

Discharge: time of discharge

The symptoms presented or reported by patients postoperatively were nausea, nausea with vomiting, dizziness, hypotension, urinary retention, shivering, constipation, bloated and diarrhea. There was no complaint of respiratory depression or gastro-intestinal upset from either groups of patients. Most of the patients complained about nausea or dizziness right after they roused out of general anesthesia at the recovery unit, and recovered spontaneously later on. Occasionally the feeling of dizziness may be continued until the second day after surgery. Some patients complained about nausea only after consumption of drink or food after the surgery. In the present study, the tramadol group was associated with a significantly higher incidence of nausea and dizziness; and a relatively higher incidence of nausea with vomiting and hypotension. 54.5% of the patients who took tramadol preoperatively were found to be hypotensive. The incidence of hypotension was not investigated or reported in some other similar research [46, 79-81], and is an issue worth investigating. Due to the high incidence of side effects observed, particularly nausea with vomiting and hypotension in the tramadol group, this study was terminated before a desired sample size could be reached.

With its unique dual mechanism of action (weak opioid agonist, and noradrenaline and 5-HT reuptake inhibitor), tramadol offers an alternative to other opioids, as these two complementary and synergistic actions enhance its analgesic effects and improve its tolerability profile [46]. Both tramadol and rofecoxib are indicated for acute pain including postoperative pain; their difference in mechanism of action may be suitable for different patients. Tramadol may be particularly beneficial in patients for whom NSAIDs are not recommended or need to be used with caution, including patients

with peptic ulcers or those predisposed to them, those with hemorrhagic disorder or hypertension, and in patients with impaired renal, hepatic or cardiac function [46]. Since selective COX-2 inhibitors do not appear to affect platelet aggregation or bleeding, it has been suggested that rofecoxib may offer some advantages in certain types of pain (e.g., surgical, dental) where bleeding is a potential complication [82].

Recently, considerable attention has been focused on the concept of preemptive analgesia. Due to CNS plasticity, conscious perception of noxious stimuli is alleged to be modified by preoperative analgesic drug administration [74]. Preemptive analgesia may prevent nociceptive inputs generated during surgery from sensitizing central neurons and, therefore, may reduce postoperative pain [82]. Although more clinical studies have been conducted to evaluate the effectiveness of different analgesia in reducing postoperative pain and analgesic requirement, the result remains inconclusive [74, 83-85]. The validity of preemptive analgesia as a routine clinical strategy can only be evaluated by more trials comparing the effectiveness of pre- or post-incision analgesia, and continuous or intermittent administration of analgesic drugs [74].

Several limitations of this study are noted. The sample size recruited for this study was too small to allow generalized conclusion to be drawn. The number of patients undergoing stapled haemorrhoidectomy in the tramadol and rofecoxib group was not equivalent (2/11 vs. 8/14). The method of haemorrhoidectomy used in different patients may vary the intensity and perception of pain. In our study, stapled haemorrhoidectomy had generally lower pain scores if compared with that of

conventional haemorrhoidectomy, this could contribute to the higher pain scores for tramadol, since the number of patients undergoing stapled haemorrhoidectomy was fewer. The absence of a control group in this study makes it difficult to assess the pain relief immediately after the operation and any differences observed in side effects between groups were solely due to the preemptive study medication or from the intra-operative analgesic and anesthetic agents administered. Future clinical studies can investigate the analgesic effects and safety profiles of different types of analgesics and their roles in preemptive analgesia.

Chapter IV – Questionnaire survey: The role of TCM in pain management

4.1 Hypothesis

This study represents the first in-depth report on the use of TCM for pain relief in Singapore. We hypothesized that TCM may play a more important role than just an alternative therapy in pain management in Singapore scenario. Our study objectives are to determine the prevalence of TCM use for pain relief, either as a first-line therapy or as an alternative to conventional analgesics and the patients' beliefs of TCM, as well as, their perceptions of healthcare professionals' attitudes and knowledge about TCM.

4.2 Materials and Methods

4.2.1 Subjects

The questionnaire survey was carried out at a TCM practitioner clinic that issues TCM therapies (Chinese proprietary medicine (CPM) and acupuncture) and two polyclinics that prescribe and dispense conventional analgesics in Singapore. These two study locations provided the convenient samples of respondents which allowed comparison of the opinions and perspectives of patients seeking treatment from practitioners with different trainings and practices at the respective study sites. The subjects were patients who visited any of these clinics for consultation, age of at least 18 years, who were prescribed conventional analgesic/s or diagnosed with any condition that was causing pain, English or Chinese language literate, and voluntarily

consented to participate in the study. For subjects attending the polyclinics, their prescriptions were screened at the polyclinic pharmacy. Prescriptions listing conventional analgesics like the NSAIDs, oral or external dosage forms, were tagged and the respective patients were approached. For those attending the TCM practitioner clinic, patients with diagnosis of existing conditions that caused pain, either acute or chronic, were informed by the TCM practitioner about our study and were approached after the consultation. Respondents were assured that all information divulged would be treated as confidential and used for research purpose only.

4.2.2 Instrumentation

A researcher-designed, self-administered, questionnaire was employed (Appendix IV). It was presented in both English and Chinese languages; respondents were allowed to choose to answer either version. It consisted of 27 questions which covered 5 sections: (a) basic demographic data; (b) information on the pain experienced (location, severity and frequency); (c) information on the used of TCM for pain relief; (d) information on the use of conventional medicines for pain relief; (e) general views on the use of TCM. Sections (c), (d) and (e) included questions pertaining to the usage of TCM or conventional medicine, perceived efficacy or side effect, cost, and their attitudes towards the use of TCM and conventional medicines. Only respondents who used TCM and/or conventional medicines for pain relief in the preceding 12 months were required to answer questions in sections (c) and/or (d). Filter questions were used at the beginning or end of the sections to direct the respondents to the relevant sections.

The severity of pain in section (b) was assessed using the Verbal Rating Scale (VRS), which consists of a list of adjectives describing the different levels of pain intensity on a 5-point scale: no pain, mild pain, moderate pain, severe pain and very severe pain. The attitude questions of sections (d) and (e) in the Likert format were used to gauge respondents' attitudes towards the use of conventional medicines and TCM. There are eight and ten items under the respective sections on attitude, with the options of "strongly disagree", "disagree", "not sure", "agree" and "strongly agree". The possible points ranged from 1 to 5, with 1 being most negative and 5 being most positive. Scores for negative statements were reversed (e.g. score 1 in a particular negative statement will be reversed to score 5) before further analysis so that the higher score reflects a more positive attitude.

A pilot study was carried out before the actual survey, involving 16 respondents from among friends and colleagues. The pilot study tested the general comprehensibility of the questions and was a source of feedback for improvements to be made to the design of the questionnaire. Ambiguous or incomprehensible questions were rephrased. The results obtained from the pilot study were excluded from the actual analysis.

4.2.3 Statistical analysis

Computer software SPSS 11.0 for windows was employed in statistical analysis. The respondents were categorized either according to the location of survey (TCM practitioner clinic or polyclinic) or usage of TCM for pain relief for the preceding 12 months (TCM user or non-user). Patients' demographic data, prevalence of TCM use

and attitude scores of each group were analyzed using bivariate analysis (Chi-square test or *t* test as appropriate). The attitude scores among different age groups, at different education levels, and of different income levels were compared by analysis of variance (ANOVA). Logistic regression analysis was then conducted to determine the relative contributions of various characteristics to the individual TCM user or non-user. Results were considered to be significant at a *p*-value of < 0.05.

4.3 Results

A total of 220 respondents from the three survey locations took part in this study: 100 attended the TCM practitioner clinic, and 120 attended the two polyclinics. Among these, 6 questionnaires were excluded from further analysis because of the high percentage of incomplete questions (at least two sections out of five were not answered, which included the critical attitude questions), yielding a total of 214 questionnaires, that is, 98 (45.8%) respondents attending the TCM practitioner clinic and 116 (54.2%) attending the polyclinics.

The basic demographic data of the respondents is shown in Table 4.1. There were 120 (56.1%) female respondents, which made up a slight majority. The average age of the respondents was 38.8 years, ranged from 18 to 70, with the majority (69.6%) of age 26 to 55 years. Most of the respondents were Chinese (80.4%). There were 13.6% of Malay respondents and about 6.1% of Indian and other races group. More than 80% of the respondents had at least attained secondary level education. A total of 35.5% had a monthly income below S$1000, 41.6% between S$1000 and S$3000, and 16.4% above S$3000 and 6.5% did not report their monthly income. The breakdown

of the respondents' demographic data according to the location of survey was also shown in Table 4.1.

Table 4.1 Demographics Data of TCM survey

Characteristics	All subjects			TCM user
	TCM practitioner clinic, No. (%)	Polyclinics No. (%)	Total No. (%)	Total No. (%)
Gender				
Female	68 (69.4)	52 (44.8)	120 (56.1)	63 (62.4)
Male	30 (30.6)	64 (55.2)	94 (43.9)	38 (37.6)
Age (in years)				
18 – 25	5 (5.1)	37 (31.9)	42 (19.6)	8 (7.9)
26 – 40	34 (34.7)	42 (36.2)	76 (35.5)	37 (36.6)
41 – 55	44 (44.9)	29 (25)	73 (34.1)	43 (42.6)
> 55	15 (15.3)	8 (6.9)	23 (10.8)	13 (12.9)
Mean ± SD	43.83 ± 10.90*	34.63 ± 12.55	38.84 ± 12.66	42.26 ± 11.05
Range	18-70	19-66		
Race/ethnicity				
Chinese	96 (98.0)	76 (65.5)	172 (80.4)	91 (90.1)
Malay	1 (1.0)	28 (24.1)	29 (13.6)	7 (6.9)
Indian	0	9 (7.8)	9 (4.2)	1 (1.0)
Other	1 (1.0)	3 (2.6)	4 (1.9)	2 (2.0)
Highest level of education				
Primary or below	27 (27.6)	8 (6.9)	35 (16.4)	25 (24.8)
Secondary	46 (46.9)	63 (54.3)	109 (50.9)	49 (48.5)
Tertiary or above	23 (23.5)	42 (36.2)	65 (30.4)	26 (25.7)
Unknown	2 (2.0)	3 (2.6)	5 (2.3)	1 (1.0)
Monthly income				
Less than S$1000	39 (37.8)	37 (31.9)	76 (35.5)	35 (34.7)
S$1000 – S$2999	35 (35.7)	54 (46.6)	89 (41.6)	37 (36.6)
S$3000 – S$5999	19 (19.4)	12 (10.3)	31 (14.5)	19 (18.8)
> S$6000	1 (1)	3 (2.6)	4 (1.9)	3 (3.0)
Unknown	4 (4.1)	10 (8.6)	14 (6.5)	7 (6.9)

* $p < 0.05$

Table 4.2 Information related to pain experience

Characteristic	TCM practitioner clinic, No. (%)	Polyclinics No. (%)	Total, No. (%)
Areas of body in pain*			
Back	31 (17.8)	40 (19.3)	71 (18.6)
Head	26 (14.9)	36 (17.4)	62 (16.3)
Shoulder	21 (12.1)	22 (10.6)	43 (11.3)
Arm (included hand and wrist)	21 (12.1)	22 (10.6)	43 (11.3)
Ankle and foot	17 (9.8)	26 (12.6)	43 (11.3)
Chest and stomach	25 (14.4)	17 (8.2)	42 (11.0)
Knee	20 (11.5)	14 (6.8)	34 (8.9)
Neck	9 (5.0)	23 (11.1)	32 (8.4)
Others	4 (2.3)	7 (3.4)	11 (2.9)
Severity of pain			
Mild pain	35 (35.7)	28 (24.1)	63 (29.4)
Moderate pain	41 (45.6)	49 (42.2)	90 (42.1)
Severe pain	11 (11.2)	27 (23.3)	38 (17.8)
Very severe pain	2 (2.0)	5 (4.3)	7 (3.3)
Unknown	9 (9.2)	7 (6.0)	16 (7.5)
Number of areas in pain			
Pain in one area	47 (48.0)	63 (54.3)	110 (51.4)
Pain in two areas	28 (28.6)	25 (21.6)	53 (24.8)
Pain in more than two areas	18 (18.4)	26 (22.4)	44 (20.6)
Unknown	5 (5.1)	2 (1.7)	7 (3.3)

*7 respondents did not indicate the areas of body in pain. Respondents may choose more than one answer.

Table 4.2 shows the overall and breakdown (according to location of survey) information related to respondents' pain experiences. The anatomical areas with pain were the back (18.6%), followed by the head (16.3%), shoulder, arms and ankle/foot (11.3%). Most rated the severity of their pain as 'moderate' (42.1%) or 'mild' (29.4%), and only 7 respondents (3.3%) rated it as 'very severe'. About 45.4% of the respondents experienced pain in two or more areas of the body and with four respondents indicating that pain was experienced in up to 6 different areas of their bodies.

Out of the 214 respondents, 101 (47.2%) indicated that they had used TCM for pain relief in the preceding 12 months (TCM user), and of these 70 were under the care of the TCM practitioner and 31 of them were polyclinic patients. The characteristics that were found to be significant for predicting whether the respondent is a TCM user or non-user, were location of survey, age range, racial, and education level. Further logistic regression indicated that the location of survey was the only item significantly related to use or non-use of TCM. There was significantly more TCM users from TCM practitioner clinic than that from polyclinic. Most of the TCM users was of the ages 26-55 (79.2%). It was found that the percentage of respondents, who were TCM users, increased with age, that is, 19%, 49%, 59% and 57% of those aged 18-25, 26-40, 41-55 and more than 55 years, respectively. This suggests that TCM was more popular in the middle-aged and older aged groups. Majority of the TCM users was Chinese and a minority (10%) was non-Chinese. Out of these 101 TCM users, 54 (53.5%) tried conventional medicines for pain relief prior to switching to TCM. In

other words, 47 (46.5%) TCM users had used TCM as a first-line pain relief in the preceding 12 months.

Table 4.3 summarizes the types of TCM used and the reasons for using TCM for pain relief. Of the treatments listed in the questionnaire, oral CPM was the most frequently cited treatment for pain relief by 74.7% of the 101 TCM users, followed by CPM for external application (31.3%), Chinese massage therapy (28.3%), acupuncture (25.3%) and raw herbs (20.2%). When asked about the reasons for using TCM for pain relief, the most common cited by 38 (55.9%) out of 68 respondents from TCM practitioner clinic was 'TCM is more effective than Western medicine'. However, for TCM users from polyclinics, 'TCM was recommended by friends or family' was the most common reason given (21, 67.7%). About 32% respondents indicated that 'TCM has fewer side effects than Western medicine'. The overall reported efficacy of TCM for pain relief was 91.1% (92 out of 101). However, seven (22.7%) out of 31 respondents from polyclinic indicated that the TCM treatments tried were ineffective, which was significantly higher than the other group (2.9% stated as not effective). Nevertheless, only one respondent from TCM practitioner clinic reported a side effect after using TCM, which was stated as 'stomachache'.

Table 4.3 Types of TCM treatments used for pain relief and the reasons

Treatment (N = 99)*	**TCM practitioner clinic (N = 68)**	**Polyclinic (N = 31)**	**Total (N = 99)**
CPM for oral consumption	57 (83.8)	17 (54.8)	74 (74.7)
CPM for external application	17 (25.0)	14 (45.2)	31 (31.3)
Chinese massage therapy	16 (23.5)	12 (38.7)	28 (28.3)
Acupuncture	15 (22.1)	10 (32.3)	25 (25.3)
Raw herbs	15 (22.1)	5 (16.1)	20 (20.2)
Reason (N=99)*			
TCM is more effective than Western medicines	38 (55.9)	6 (19.4)	44 (44.4)
TCM was recommended by friends or family	22 (32.4)	21 (67.7)	43 (43.9)
TCM has fewer side effects than Western medicines	25 (36.8)	6 (19.4)	31 (31.6)
TCM is reasonably priced	6 (8.8)	3 (9.7)	9 (9.1)
TCM is easily accessible	3 (4.4)	3 (9.7)	6 (6.1)

* Two respondents failed to give a response. Respondents may choose more than one answer.

4.3.1 Use of conventional medicines for pain relief

Patients who indicated that they had used conventional medicines for pain relief in the preceding 12 months were required to answer questions related to the use of conventional medicines for pain relief in section (d). This group of patients (122 out of a total of 214) was prescribed analgesics like paracetamol (alone or with low dose opioid analgesic), NSAIDs, or a muscle relaxant for pain relief.

An 8-item Likert format question was used in section (d) to investigate the respondents' attitudes towards the use of conventional medicines to treat pain problem (Table 4.4). The scoring system for these items was designed such that the higher score indicates a more positive attitude. When the respondents were categorized according to the location of survey, polyclinic patients score significantly higher than that of TCM practitioner clinic's patient for statements 2, 3, 7 and 8 (P = 0.02, 0.03, 0.02 and 0.02). When the respondents were re-categorized into TCM users and non-users, significant differences were found between the groups for statements 2, 3 and 8 only (P =0.022, 0.001 and 0.032). These results suggest that, the respondents from polyclinic and those TCM non-users had more positive perceptions than the respective counterparts that conventional medicines are effective in relieving pain, giving minimal side-effects with reasonable price. Moreover, polyclinic patients had higher confidence in conventional medicines for pain even if there is little research done to prove their effectiveness and safety.

Table 4.4 Mean scores for statements on the use of conventional medicines and for statements on the general use of TCM

Attitude statements towards the use of conventional medicines for pain relief	Mean Score			
	TCM practitioner clinic	Polyclinic	TCM user	TCM nonuser
1. I feel less pain after taking the medicine.	3.56	3.82	3.59	3.81
2. The medicine is effective. I feel no pain after I take the medicine for 2 days or more. (Reversed)	2.82*	3.46	2.92*	3.39
3. I feel better after taking the medicine and experience no side effects like stomach discomfort. (Reversed)	3.18*	3.76	3.12*	3.82
4. I am aware of the possible side effects that I may experience while taking the medicine.	3.54	3.19	3.47	3.24
5. I do not find taking the medicine at fixed timings (e.g. morning, noon and night) troublesome. (Reversed)	3.16	3.22	3.10	3.27
6. I stop taking the medicine regularly every day when I don't feel any pain. (Reversed)	3.78	3.76	3.78	3.76
7. I will still take Western medicines for pain relief even if there is little research done to prove their effectiveness and safety.	2.60*	3.22	2.75	3.12
8. The price of Western medicines for treatment of my pain is reasonable.	2.74*	3.4	2.86*	3.31
Attitude statements towards general use of traditional Chinese medicines				
1. Traditional Chinese medicines are safer than Western medicines.	3.64*	2.82	3.55*	2.90
2. Traditional Chinese medicines are more effective than Western medicines for treating illnesses.	3.55*	2.82	3.50*	2.87
3. It is safe to use both traditional Chinese and Western medicines together.	2.58	2.43	2.48	2.52
4. The recent Slim 10 issue [86] has not made me doubt the safety of traditional Chinese medicines. (Reversed)	3.48*	2.66	3.31*	2.82
5. I will still take traditional Chinese medicines even if there is little research done to prove their effectiveness and safety.	3.59*	2.86	3.51*	2.93
6. When asked by the pharmacist/Western doctor, I am willing to say that I am taking traditional Chinese medicines. (Reversed)	3.55	3.69	3.60	3.64
7. I see the need for the pharmacist/Western doctor to know that I am taking traditional Chinese medicines. (Reversed)	3.47*	3.80	3.48*	3.79
8. I feel that the pharmacist/Western doctor agrees with the use of traditional Chinese medicines for the treatment of any kind of illness. (Reversed)	2.76*	3.14	2.71*	3.18
9. I feel that the pharmacist/Western doctor is knowledgeable about traditional Chinese medicines. (Reversed)	2.59*	2.96	2.68	2.88
10. I would approach a pharmacist/Western doctor to find out if I can take both Western and traditional Chinese medicines together.	3.11*	3.69	3.22*	3.58

* $p < 0.05$

1= strongly dis agree; 2= disagree; 3= not sure; 4= agree; 5= strongly agree.

No significant difference was found between males and females on their attitude scores. ANOVA test failed to show differences among respondents of different age groups, education levels and income levels.

4.3.2 General views on the use of TCM

Section (e) aims to examine the respondents' general views on the use of TCM. All respondents would be required to answer questions in this section. When asked if they would use TCM first before consulting the Western medical practitioner or trying conventional medicines for treatment of any illness, 57 (26.6%) indicated that they would use TCM first and 144 (67.3%) indicated that they would not. Out of the former 57 respondents, 37 (64.9%) of them were from the TCM practitioner clinic, and 43 (75.4%) of them were TCM user. This suggests that patients from TCM practitioner clinic and those who tried TCM before would be more likely to use TCM as first-line therapy when they were sick than their counterparts ($p < 0.05$ for both cases).

A group of 39 (18.2%) out of 214 respondents stated that they were currently taking both TCM and Western medicine for pain relief. Of these, 28 (71.8%) of them were TCM users. This suggests that respondents who used TCM before were more likely to take both kinds of medicines for pain relief than the TCM non-users ($p < 0.05$).

A 10-item Likert format question was used in this section to examine the respondents' general attitudes towards the use of TCM (Table 4). When the respondents were categorized according to the location of survey, the group from TCM practitioner

clinic had a significantly higher score than that from the polyclinic group for statements 1, 2, 4 and 5 ($P = 0.001$ for all four statements); whereas polyclinic group had a significantly higher score for statements 7-10 ($P = 0.023$, 0.004, 0.006 and 0.001 respectively) . The respondents were then re-categorized into TCM users and TCM non-users; TCM user score significantly higher than that of TCM non-user for statements 1, 2, 4 and 5 ($P = 0.001$ for all four statements); whereas TCM non-users score significantly higher for statements 7-10 ($P = 0.033$, 0.001 and 0.014).

The results above suggest that, the respondents from TCM practitioner clinic and those who were TCM users have fewer concerns about the safety and efficacy of TCM than their counterparts. They showed more confidence in TCM even if there is little research done to prove their effectiveness and safety. But, all respondents (regardless of grouping) had more negative perceptions that concurrent use of TCM and conventional medicine is safe; and indicated that they would inform their pharmacists or doctors that they were using TCM only if they were asked. On the other hand, respondents from polyclinics and TCM non-users were more willing to inform the pharmacist/doctor that they are using TCM. They also felt that these healthcare professionals would support their use of TCM and they would be more inclined to approach them to find out if it would be safe to consume TCM and conventional medicines together. However, all respondents felt that pharmacists/doctors have limited knowledge of TCM.

No significant difference was found between males and females on their attitude scores towards the general opinion of TCM. ANOVA test failed to show differences

among respondents of different age groups, education levels and income levels on the attitude scores.

4.4 Discussion

The prevalence of TCM use for pain relief in the preceding 12 months by the study subjects was approximately half (47%, 101/214), with oral CPM representing the most popular choice. It was found that most of the TCM users were from the middle to old age-group, and majority of them was Chinese. This finding is consistent with other studies that older respondents were more likely to use TCM/CHM [87, 88]. It has been suggested that TCM/CHM use was significantly associated with the presence of chronic medical conditions, such as rheumatism, lower back pain or cancer, which are more prevalent in elderly. This is also within the inclusion criteria for pain-related problems of our survey thus contributing to our results.

Half (53.5%, 54/101) of the TCM users identified tried conventional medicines for pain relief prior to TCM, whereas the other half (46.5%, 47/101) used TCM as a first-line treatment for pain. This figure implies that the role of TCM in Singapore is far more than a complementary or alternative medicine, but is one of the mainstream therapies, integrated into daily lives. These findings may be very different from that of Western or European countries, where TCM remains a complementary medicine; but is believed to be similar to other Asian countries with substantial Chinese populations. Taking Hong Kong as example, the use of TCM has been a long practice in Hong Kong. It has been reported that, about 13.5% of the randomly selected sample had been using TCM drugs frequently or occasionally [87]. Respondents who

attended the TCM practitioner clinic and TCM users had a more positive orientation towards TCM, were more confident about the safety and efficacy of TCM. This perception may be due to their past experiences with TCM, which were positive with minimal side effects. Despite having a highly perceived efficacy, concerns associated with the use of TCM, especially CHM, remain. This finding is similar to other studies where respondents perceived CHM as "milder and does not have as strong side effects as Western medicine" [89]. Although it is true that CHM comes mainly from plants that is a natural source, but the 'natural source' should not be taken as equal to 'milder, less toxic or free from adverse effect'. The adverse effects of CHM include the toxicity of the herbs itself and the toxic effects due to the contaminants. A number of toxic herbs are still commonly used in CHM. Kam and Liew [90], in their review article, reported adverse effects of CHM involving the cardiovascular, neurological, gastrointestinal, hematological and renal systems. The other area of concern is the adulteration or contamination of CPM as outlined in Koh and Woo's review [91] on the presence of excessive toxic heavy metals and undeclared drugs in CPM in Singapore between 1990 and 1997. Among the 2080 CPMs screened, 42 were found to contain excessive amounts of arsenic, copper, lead and mercury; and 32 had adulterants of 19 conventional drugs (which includes antihistamine, NSAIDs, analgesic antipyretics, corticosteroid etc.). Hence, new regulations on the control of CPM were enforced in Singapore on September 1999, which included the licensing and labeling requirements and control of microbial contamination. The adverse effects of CHM may be associated with hypersensitivity reactions, resulting from long-term use at inappropriate dosage levels [92]. Therefore the public needs to be informed about the importance of consulting a qualified and experienced TCM practitioner, and should

refrain from self-medicating freely with CHM or CPM, which may delay the treatment and lead to further complications of the illness.

It was found that all respondents were more negative regarding the statement 'it is safe to use both TCM and conventional medicine together'. It suggests that the respondents might be aware of the potential risk involved with the concurrent use of TCM, especially CHM/CPM, and conventional medicine. Nevertheless, some 18% of respondents revealed that they were taking both kinds of medicine for pain relief at the time of the study. Besides, it may be common for patients, especially those with chronic diseases or cancer, to take both conventional medicine and complementary medicine (be it CHM or other therapy) together. This may expose them to the potential interactions between the complementary and conventional medicines. The interactions between CHM and both warfarin and digoxin are widely reported [90, 93-95]. The anticoagulant effect of warfarin can be potentiated by Danshen and Dong Quai (Angelica sinensis); and ginseng has been shown to decrease the effect of warfarin and to increase digoxin levels.

This study showed that most of the respondents were willing to inform to their doctor/pharmacist that they were using TCM when asked. Some respondents, especially those from the TCM practitioner clinic, do not see the need for the conventional healthcare provider to be informed that they are using TCM. This group also thought that their doctor/pharmacist would not approve of the use of TCM. Therefore it is unlikely that patients would take the initiative to discuss this issue with the pharmacist/doctor. It is important for the healthcare professional to establish

relationships that allow effective communication with the patients [89] and to reassure the patients that the aim is not to reprimand them for bad health practices, but to offer useful information on the management of health conditions [95]. Then patients who have concerns about their treatments can surface and discuss them with their doctor/pharmacist in order to avoid adverse events and any potential interaction.

For the pharmacist/doctor to be able to advise their patients on the use of CHM, they need to be well-informed. Knowledge regarding the benefits, limitations and side effects of CHM would be useful, and more importantly, the possible interactions between conventional and traditional medicines [95]. Limited knowledge on TCM often breeds fear that all such treatments would yield more risks than benefits to the patients. All our respondents felt that the doctor/pharmacist have limited knowledge of TCM. Another study also found that fellow doctors had the same knowledge level as the patients on TCM [96]. This raises the need to incorporate knowledge of TCM in the curricula of the pharmacy and medical undergraduate programs or as continuing education for healthcare practitioners. TCM and conventional medicine independently employ very different approaches of treating disease, from the basic theories and concepts, to the therapeutic principles and the corresponding treatments.

Several limitations to this study are noted. As the questionnaire was designed for self-administration, patients who were illiterate were unable to answer the questionnaire by themselves, and thus were excluded from the study. They were mainly the elderly and some foreign workers. The exclusion of the elderly group of patients might have resulted in the loss of a substantial number of patients who were susceptible to pain and aches, and who were more likely to use TCM as suggested by another study [55].

Some respondents commented that the questionnaire was too lengthy; especially the two Likert format questions which involved 8 and 10 items, that they had no time to read the statements carefully, leaving some questions unanswered. There were also problems with language and translation of the questionnaire. The translated Chinese version may not be absolute similar to the English version although efforts were made to ensure that the same meanings were conveyed. This could have led to misinterpretation of the questions.

This study allows for a better understanding of some types of TCM treatment in Singapore. Some areas of concern associated with TCM use, such as the lack of awareness about the safety of CHM, as well as, the cautions needed for the concurrent use of CHM and conventional medicine have been highlighted. As the healthcare professionals and their patients become more knowledgeable and aware of possible adverse reactions and complications that can arise from these treatments, overall patient safety can be further enhanced.

Chapter V – Conclusion

Pain is a very common complaint presented by patients, and it represents the most commonly perceived symptom which has an enormous impact on public health which is worthy of more attention. There are many modalities that can be used in pain management; nonetheless, drug treatment remains, for the most part, the cornerstone of treatment. While opioids remain an integral part of pain-management strategies, there is now an emphasis on the use of adjuvant drugs, such as NSAIDs, COX-2 inhibitors and tramadol, which acts through different mechanisms. On the other hand, traditional, complementary and alternative medicines are becoming increasingly popular throughout the world and gaining greater acceptance in the healthcare system. TCM, a kind of traditional medicines which is popular in local setting, is believed to have a part to play in pain management. The three different studies described in previous chapters look into various aspects in pain management, namely the concept of "preemptive analgesia" in postoperative pain management, and the role TCM in acute or chronic pain management in a local scenario.

The preemptive analgesic effects of celecoxib, etoricoxib, indomethacin, naproxen and tramadol in a rat model of incisional pain were studied by comparing the withdrawal thresholds and cumulative pain scores between the control, preoperative and postoperative groups which were administered with different drugs. The findings showed that animals that were given preoperative administration of these 5 drugs exhibited significantly higher withdrawal thresholds than that of the placebo control

group. Moreover, the effects of preoperative administration of etoricoxib, indomethacin, naproxen and tramadol were significantly higher compared to that of postoperative administration of the corresponding drug for a period up to 2 days after the surgery. The preemptive analgesic effects of these five drugs in animal work are encouraging, and future studies on the combination of preemptive analgesia and multimodal analgesic strategy, multi-dose regimen trial and randomized controlled clinical trial will be needed to corroborate the clinical relevance of preemptive analgesia.

The analgesic efficacies and safety profiles of preoperative rofecoxib and preoperative tramadol in patients undergoing haemorrhoidectomy were studied at an ambulatory surgical centre. Both rofecoxib and tramadol showed comparable analgesic efficacy in this study. However, tramadol was associated with a higher incidence of side effects. Future clinical trials with proper study design will be needed to investigate both the analgesic efficacy and safety profiles of different types of analgesics and their roles in preemptive analgesia. The idea of preemptive analgesia is attractive, if it is proven to be clinically sound, improvement in patient comfort, decrease in postoperative morbidity and potential healthcare saving could then be anticipated.

In Singapore, conventional medicine is still the orthodox therapy which is endorsed by the national healthcare institutions. Nevertheless, the results from this survey reveal that the use of TCM to treat pain problem is prevalent, with substantial of them, especially the ethnic Chinese, using TCM as first-line therapy. The survey revealed that the total prevalence of TCM use for pain relief in the preceding 12 months by the study subjects was 47%. A 46.5% of these TCM-users used TCM as the first-line treatment

for pain relief, suggesting that TCM is more than just an alternative medicine in Singapore, and perhaps in other countries where the ethnic Chinese lives, although further study is required to conclude these. This study seeks to understand aspects of TCM treatment in Singapore. The results also revealed areas of concern associated with TCM use, safety being the main priority. More research needs to be conducted to establish the potential risks arising from interactions between the concurrent use of CHM and conventional medicines. Pharmacovigilance efforts and directions should be expanded to include TCM treatments so that the evidence of safety and risk with East-West combination treatments can be gathered expediently over time. Moreover, greater effort towards public education on the safety and efficacy of the use of TCM is warranted. Doctors and pharmacists should be further equipped with relevant knowledge in order to provide education and information to patients

Several limitations in these studies were noted. The relatively small sample size and the convenient samples that involved in the clinical study and the questionnaire survey have limited their generalisability to represent the population at large. In order to draw conclusions that apply to general population, a representative sample with large enough sample size from this study population would be required. Bias is one of the main concerns in any clinical trial. Both the animal and clinical studies described were not double blinded; investigator bias could have been introduced during the data collection and assessment stage. In the animal study, the parameters used in clinical appearance investigation of the rats are always subjective and varies considerably. The signs of pain may be very subtle and strongly depends on the experience of the investigator. The investigators bias would impose some limitation to our study. Future study with proper

study design, preferably double blind study with representative sample size, would be required to avoid potential problems of bias. No pharmacoeconomic analysis was done in any of our studies. It would be interesting to involve cost-effectiveness study of various treatments in a future study, for example, preemptive analgesic treatment versus postoperative analgesic treatment among different drugs; and TCM versus conventional treatment. The pharmacoeconomic information will be precious in determining the most efficient and economic treatment in pain management.

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Appendices

Appendix I – Numerical Score Sheet for Pain Study Using Rat Model

Date: Time: Day:

Group: / ID	1	2	3	4	5	6
Parameter						
Weight bearing* 1 (0-2)						
Weight bearing 2 (0-2)						
Weight bearing 3 (0-2)						
Body weight score† (0-3)						
Eyelid closure‡ (0-2)						
General grooming (0-2)						
Ocular/nasal discharge (0-2)						
Vocalization (0-2)						
Biting/licking wound (0-2)						
Overall activity (0-2)						
Provoked activity (0-2)						
Diarrhea/abnormal discharge (0-2)						
Total pain score (0 - 25)						

* Weight bearing score:
Each animal was closely examined for a period of 1- minute and scored accordingly. The observation was then repeated twice with a 3-5 minute test-free period between each trial.
0 – Full weight bearing of the foot, the wound was blanched or distorted by the mesh;
1 – Half weight bearing, the would touched the mesh without blanching or distorting;
2 – No weight bearing, the foot was completely off the mesh;

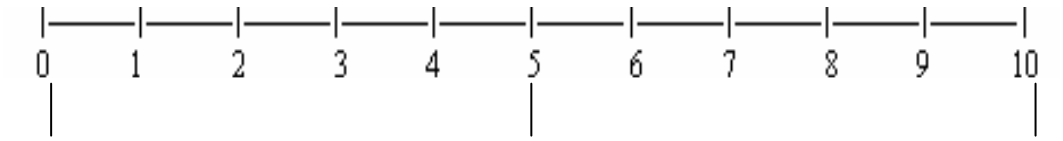
† Body weight score:
0 – Normal, less than 5% weight loss
1 – 5-10% weight loss
2 – 11-20% weight loss
3 – More than 20% weight loss

‡ For other parameters:
0 – Normal
1 – Minor abnormalities
2 – Serious abnormalities

Appendix II – Numerical Rating Scale (NRS)

Numerical Rating Scale (NRS)

Please indicate the number that best corresponds to the pain you are feeling now.



No pain
? ?
Tidak ada kesakitan

Moderate pain
? ? ? ?
Kesakitan yang serdahana

Worst possible pain
? ? ? ?
Kesakitan yang terlalu teruk

Appendix III – Verbal Rating Scale (VRS)

Verbal Rating Scale (VRS)

Please indicate which of the following categories most closely describe the pain you are feeling now.

No pain ? ? Tidak ada kesakitan
No pain at rest, slight pain on movement ? ? ? ? ? , ? ? ? ? ? ? ? Tidak ada kesakitan ketika berehat, sedikit kesakitan ketika bergerak
Slight pain at rest, moderate pain on movement ? ? ? ? ? ? ? , ? ? ? ? ? ? ? Sedikit kesakitan ketika berehat, kesakitan yang sederhana ketika bergerak
Moderate pain at rest, severe pain on movement ? ? ? ? ? ? ? , ? ? ? ? ? ? ? Kesakitan yang sederhana ketika rehat, kesakitan yang keterlaluan ketika bergerak
Severe pain at rest and on movement ? ? ? ? ? ? ? ? ? ? ? Kesakitan yang keterlaluan ketika rehat dan ketika bergerak

Appendix IV – TCM Survey Questionnaire

Founded 1905

THE NATIONAL UNIVERSITY OF SINGAPORE

Dear Sir/Madam,

The National University of Singapore is conducting a survey to study the use of traditional Chinese medicines for pain relief and the opinions of the public on the use of traditional Chinese medicines in general.

We would like to invite you to participate in this survey by completing the following questionnaire. The questionnaire consists of 27 questions and would take approximately 15 minutes to complete. If you agree to participate in this survey, please be assured that all information received will be strictly confidential and used purely for research purposes.

Thank you very much for your patience and kind understanding.

Location of survey :_____

A. Personal Details

Please fill in your name, occupation and year of birth in the space provided.

1. Initials of your name :_____
2. Occupation :_____
3. Year of birth :_____

Please tick the most appropriate choice:

4. Gender

   Male ☐ Female ☐

5. What is your ethnicity?

   Chinese ☐ Malay ☐

   Indian ☐ Others:_____ (Please specify)

6. What is your highest level of education attained?

Primary	☐	Pre-university/Junior college	☐
Secondary	☐	Tertiary	☐
Polytechnic	☐	No formal education	☐
Others:_____ (Please specify)			

7. What is your monthly income?

Less than S$1000	☐	S$3000 – S$5999	☐
S$1000 – S$2999	☐	S$6000 and above	☐

8. Which language do you normally speak (at home, with family and friends, etc)?

English	☐	Mandarin	☐
Malay	☐	Tamil	☐
Chinese dialect (E.g. Hokkien, Teochew, Cantonese, etc)	☐	Others:_____ (Please specify)	☐

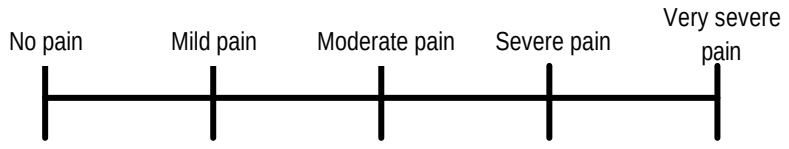
B. About your pain

9. In which part of your body do you experience pain? **(You may tick more than once)**

Head/Forehead	☐	Face	☐
Shoulder	☐	Wrist	☐
Joints of fingers	☐	Elbow	☐
Back	☐	Abdomen	☐
Thigh	☐	Knee	☐
Feet (including the sole)	☐	Ankle	☐
		In the neck	☐
Others:_____ (Please specify)	☐		

10. How severe is your pain?

Please circle the choice that best describes the pain you experience.



Please tick the most appropriate choice for the following questions:

11. Do you feel the pain almost everyday or every other day?

Yes	☐	(If **Yes**, please go to question 12)
No	☐	(If **No**, please go to question 13)

12. For how long have you been feeling the pain? **(Please fill in your answer in the space provided)** (E.g. For weeks, months or years)

_____

_____

13. What was the cause of your pain? **(Please fill in your answer in the space provided)** (E.g. Operation/surgery, injury from work, fell down, etc)

_____

_____

14. Did you use any traditional Chinese medicine in the **past 12 months** for pain relief?

Yes ☐ (If **Yes**, please go to question 15)

No ☐ (If **No**, please go to question 21)

C. Use of traditional Chinese medicine for pain relief

In this survey, traditional Chinese medicine refers to raw herbs, ready-made herbal products for oral consumption or external use, acupuncture and massage therapy used in the system of therapeutics according to traditional Chinese method.
Ready-made products refer to patent herbal products either for oral consumption or external use, and medicated plasters with herbal ingredients.

15. What type(s) of traditional Chinese medicine have you used for pain relief?

(You may tick more than once)

Raw herbs ☐

Acupuncture ☐

Massage therapy ☐

Others:_____ ☐

(Please specify)

Ready-made medicine for oral consumption ☐

Ready-made medicine for applying on the skin ☐

skin (E.g. Liniments, creams, herbal plasters)

16. Is the traditional Chinese medicine you have used effective in pain relief?

Yes ☐

No ☐

17. Did you feel worse in any way after using the traditional Chinese medicine?

Yes ☐

No ☐

If **Yes**, can you describe how you felt? _____

Note: Western medicine includes orally taken preparations like **tablets and liquid syrups**, and externally applied ones like **creams, ointments, gels and medicated plasters** (E.g. Tokuhon, Salonplas).

18. What are your reasons for using traditional Chinese medicine for pain relief?
(You may tick more than once)

Easy to buy Chinese medicine	☐	Traditional Chinese medicine has less side effects than Western medicine	☐
Recommended by friends or family	☐		
Reasonably priced	☐	Chinese medicine is more effective than Western medicine	☐
Others:_____ (Please specify)	☐		

19. How much do you spend each month on traditional Chinese medicine for pain relief?

Less than S$10	☐	S$10 – S$25	☐
S$26 – S$45	☐	More than S$45	☐

20. **Before** using traditional Chinese medicine, did you see a Western doctor or use any Western medicines for pain relief?

Yes	☐	(If **Yes**, please go to question 22)
No	☐	(If **No**, please go to question 25)

D. Use of Western (conventional) medicine for pain relief

21. **In the past 12 months**, have you seen a Western doctor or used any Western medicine(s) for pain relief?

Yes	☐	(If **Yes**, please go to question 22)
No	☐	(If **No**, please go to question 25)

22. What Western medicine(s) have you used for pain relief?

_____

_____

23. How much do you spend each month on Western medicine(s) for pain relief?

Less than S$10	☐	S$10 – S$25	☐
S$26– S$45	☐	More than S$45	☐

24. Below are some statements about the **treatment of pain using Western medicine**. Please **read** the statements **carefully** and circle the number that best describes **how you feel**.

Statements	Strongly disagree	Disagree	Not sure	Agree	Strongly agree
1) I feel less pain after taking the medicine.	1	2	3	4	5
2) The medicine is ineffective. I still feel the pain even after I take the medicine for 2 days or more.	1	2	3	4	5
3) I feel worse after taking the medicine because of side effects like stomach discomfort.	1	2	3	4	5
4) I am aware of the possible side effects that I may experience while taking the medicine.	1	2	3	4	5
5) I find taking the medicine at fixed timings (e.g. morning, noon and night) troublesome.	1	2	3	4	5
6) I take the medicine regularly every day even when I don't feel any pain.	1	2	3	4	5
7) I will still take Western medicines for pain relief even if there is little research done to prove their effectiveness and safety.	1	2	3	4	5
8) The price of Western medicines for treatment of my pain is reasonable.	1	2	3	4	5

E. General views on the use of traditional Chinese medicine

25. Do you usually use traditional Chinese medicine first before seeing a Western doctor/use Western medicine for any illness you have?

Yes ☐
No ☐

26. Are you currently taking both Western and traditional Chinese medicine for pain relief?

Yes ☐
No ☐

27. Below are some possible **opinions** that the general public may have about the **use of traditional Chinese medicine**. Please **read** the statements **carefully** and circle the number that best describes **how you feel**

Statements	Strongly disagree	Disagree	Not sure	Agree	Strongly agree
1) Traditional Chinese medicines are **safer** than Western medicines.	1	2	3	4	5
2) Traditional Chinese medicines are **more effective** than Western medicines for treating illnesses.	1	2	3	4	5
3) It is safe to use both traditional Chinese and Western medicines together.	1	2	3	4	5
4) The recent Slim 10 issue has made me doubt the safety of traditional Chinese medicines.	1	2	3	4	5
5) I will still take traditional Chinese medicines even if there is little research done to prove their effectiveness and safety.	1	2	3	4	5
6) When asked by the pharmacist/Western doctor, I am unwilling to say that I am taking traditional Chinese medicines.	1	2	3	4	5
7) I see no need for the pharmacist/Western doctor to know that I am taking traditional Chinese medicines.	1	2	3	4	5
8) I feel that the pharmacist/Western doctor **disagrees** with the use of traditional Chinese medicines for the treatment of any kind of illness.	1	2	3	4	5
9) I feel that the pharmacist/Western doctor knows very little about traditional Chinese medicines.	1	2	3	4	5
10) I would approach a pharmacist/Western doctor to find out if I can take both Western and traditional Chinese medicines together.	1	2	3	4	5

-- END --